Outcome after vascular surgery in the ageing

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CONTENTS

CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THIS THESIS

Cardiovascular disease is a common problem in the general population, affecting an essential part of adults over the age of 60 years. Among the multiple risk factors established for cardiovascular disease, high age remains one of the strongest predictors for a cardiovascular event.[1,2] Also the prevalences of peripheral arterial disease, carotid artery disease and abdominal aortic aneurysms increase with age.[3-5] With the elderly population increasing at an unprecedented rate, the number of surgical procedures in the elderly will increase in the future. This increase in elderly patients requiring appropriate health care brings specific problems and challenges with it.

In vascular surgery there are specific age-related issues that are, in an ageing population, increasingly important. For example, as abdominal aortic aneurysm (AAA) is an age-related disease, more elderly patients, including octo- and even nonagenarians, will be referred for AAA management. However, open AAA repair in these age groups is associated with high morbidity and mortality rates.[6-11] Endovascular repair (EVAR) could potentially offer substantial benefit although the procedure still raises questions and sometimes even is shrouded in controversy. Although the goal of AAA repair is to prevent rupture, the risk of rupture in this group with a limited life expectancy must be balanced against the risk of the procedure. Further, one must consider effects on quality of life. Even if mortality rates are acceptable, decrements in such issues as mobility and self-care must be considered.

The same applies for carotid endarterectomy (CEA) for selected patients with symptomatic carotid stenosis in order to prevent ischemic strokes or death. In various clinical trials and meta-analyses it has been proven a superior treatment compared to medical therapy alone. In the past advanced age has been associated with an increased risk for complications after CEA.[12-16] Although most studies are reporting results of octogenarians as high risk group, there is even evidence that increased risk already starts at the age of 70.[17,18] In all it seems clear that there is a significant interaction between age and the treatment risk of stroke and/or death after carotid artery revascularization and it must be taken into account when considering elderly patients for surgery.

However, when considering surgery in elderly patients there are more factors, besides the increased perioperative risk, that should be taken into account. Vascular surgery patients are among patients at highest risk for developing postoperative delirium (POD). While this appears to be caused by the fact that vascular patients are both old and frail and usually present with multiple comorbidities, including cerebrovascular disease, atherosclerosis appears increasingly important. POD is not only the most common complication in elderly (> 65 years) patients, affecting approximately 11-60% during hospital admission, it is also associated with short-term effects such as prolonged hospitalization and institutionalization (due to functional loss, loss of independence and the inability to return to ones home) and increased medical costs. However, also long-term effects such as persistent functional decline and death have been associated with POD[19-26]. Although POD can occur after most vascular surgery procedures, the highest incidences are found in abdominal aortic surgery (46-52%).[27] With the increasing life expectancy the incidence of POD is also likely to increase unless preventive strategies are developed. Unfortunately, very few studies focus on risk factors and delirium prevention among vascular surgery patients and an accurate pre-screening tool is currently lacking.[28-31]

Aims and outline of this thesis

With an already limited life expectancy the benefit of reducing post-operative morbidity and mortality and maintaining a good quality of life seems applicable to elderly patients but specifically to octogenarians. In this thesis we attempted to clarify and answer specific questions that are of importance in treating octogenarians in vascular surgery and questioned whether the patient's age alone should affect a vascular surgeon's management algorithm. Here we have specifically focused on patients who were operated on an abdominal aneurysm or a carotid stenosis. We have focused our attention on these two groups because it is these patients which are frequently called into question whether an intervention may still be worthwhile.

This thesis is divided into two sections. In **Section I** we focused on the outcome of aneurysm repair and carotid revascularisation in octogenarians. **Section II** covers a detailed investigation on POD among vascular surgery patients, including a prospective study on POD prevention. In more detail, **Chapter 2** focuses on the question whether advanced age may be considered a factor to refrain from further treatment and ICU admission and whether this holds true for octogenarians suffering from a ruptured AAA (rAAA). With the steady increase of elderly patients in surgical practice, more and more elderly patients will present with a ruptured aneurysm. In this study we focus both on short and long term outcome as well as procedure related morbidity and mortality. In **Chapter 3** the question is extended by using a large database to test the hypothesis that octogenarians suffering from AAA may be safely treated in an elective setting with EVAR, while still providing acceptable post-procedure quality of life.

Elaborating on the chapters on AAA, in **Chapter 4** a study was undertaken to evaluate whether age alone should be a valid reason to abstain from treating octogenarians with a carotid stenosis by means of carotid endarterectomy (CEA). In the past advanced age has been associated with an increased risk for complications after CEA. In all it seems there is a significant interaction between age and the treatment risk of stroke and/or death after carotid artery revascularisation. As it becomes increasingly clear that elderly patients are unsuitable for carotid artery stenting (CAS), determining the outcome after CEA in this vulnerable group is becoming even more important.

In **Section II** we focus more on patient-related risk factors surrounding surgery and aimed in particular at post-operative delirium (POD). For elderly patients admitted to the hospital POD is a common and important complication. Although various risk factors have already been identified, to date the true etiology of POD is very unclear. Compared to the general patient population vascular patients, and in particular elderly patients, are characterized by systemic atherosclerosis. We therefore hypothesized that atherosclerosis, as common factor, is the main cause of the increased risk of POD in vascular surgery patients. In **Chapter 5** we present a review designed to identify prognostic factors for the occurrence of POD within the field of vascular surgery. The main question was to determine whether atherosclerosis as such may be considered a risk factor for POD.

During the literature analysis for **Chapter 5** it became clear that pre-emptively predicting POD proved to be very difficult. A preoperative tool for risk assessment is unfortunately not yet at hand. Nevertheless, the treatment of POD begins by preventing its occurrence. Following our primary analysis we set up a prospective cohort study in **Chapter 6** to determine whether a standardized frailty score (Groningen Frailty Indicator; GFI) had a positive predictive value for POD and other surgical complications in vascular surgery patients and could potentially be used as a screening tool to identify patients at high risk for POD.

Next to the predictive power of the GFI in the previous study, it became clear that inflammation appears to play an important role in the occurrence of POD. Based on these findings we specifically looked at C-reactive protein (CRP) as biomarker for the development of POD following vascular surgery in **Chapter 7**.

Chapter 8 and 9 conclude this thesis, providing a general discussion and summary of the findings of this thesis.

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SECTION I

OUTCOME OF VASCULAR SURGERY IN OCTOGENARIANS.

CHAPER 2

EFFECTIVENESS OF TREATMENT FOR OCTOGENARIANS WITH ACUTE ABDOMINAL AORTIC ANEURYSM

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ABSTRACT

Objective

To investigate whether advanced age may be a reason to refrain from treatment in patients with an acute abdominal aortic aneurysm (AAAA).

Materials and Methods

This was a retrospective cohort study that took place in a tertiary care university hospital with a 45-bed intensive care unit. Two hundred seventy-one patients with manifest AAAA, admitted and treated between January 2000 and February 2008, were included. Six patients died during operation and were included in the final analysis to ensure an intention-to-treat protocol, resulting in 234 men and 37 women with a mean age of 72 ± 7.8 years (range, 54-88 years). Forty-six patients (17%) were 80 years or older. Interventions involved open or endovascular AAAA repair.

Results

Mean follow-up was 33 ± 30.4 months (including early deaths). Mean hospital length of stay was 16.9 ± 20 days for patients younger than 80 and 13 ± 16.7 days for patients older than 80 years of age. Kaplan Meier survival analysis revealed a significantly better survival for the younger patients ($p < .05$). Stratification based on urgency or type of treatment did not change the difference. Two-year actuarial survival was 70% for patients younger than 80 and 52% for those older than 80. At 5 year follow-up, these figures were 62% and 29%, respectively. Mean survival in patients older than 80 was 39.8 ± 6.8 months versus 64.5 ± 3.0 months in those younger than 80. Main complications were disease related with no statistical differences between the younger (< 80 years of age) and older (≥ 80 years of age) group.

Conclusions

For octogenarians, our liberal strategy of treating patients with AAAA was associated with satisfactory short and long-term outcome, with no difference with regard to disease or procedure related morbidity between the younger and older group. Assuming an integrated system for managing AAAA is in place, advanced age is not a reason to deny patients surgery.

Introduction

The incidence of abdominal aortic aneurysms (AAA) treated both en elective and acute setting, has significantly increased over the past decade.[1] Also, population screening programs for AAA, such as single duplex ultrasound scanning in men older than 65 years of age, are being instituted in many centres as a way to reduce the total mortality in acute AAA (AAAA).[2,3] At the same time, the population in most Western countries is ageing rapidly, and therefore an increasing number of octogenarians are being referred for AAA intervention and subsequent ICU admission. Interventions may be planned on an elective basis, but a substantial part will still be carried out as an emergency intervention, once the aneurysm has progressed to an AAAA. Acute aneurysms may be categorized into acute non-ruptured or so-called symptomatic aneurysms (sAAA) and acute ruptured (rAAA). Obviously, results from rAAA repair are poorer than those from sAAA repair, but they tend to vary widely in literature, and are also dependent on the treatment modality used (open or endovascular repair). Even though there has been an increased awareness with earlier diagnosis and treatment, a meta-analysis of open repair of ruptured aortic abdominal aneurysms (rAAA) demonstrated an overall mortality of 49% over the last 15 years, with no significant change over time.[4] In our own report designed to define cost-effectiveness of the introduction of a preferential endovascular strategy in patients with AAAA, we found that in-hospital mortality dropped from 31% (historical open repair control group) to 18% (for endovascular repair of selected patients).[5] These results compare well with the literature and resulted in a local treatment strategy in which patients were virtually never denied treatment, regardless their age.

On the other hand, as in many European countries, in the Netherlands too there is a rapidly increasing demand for health care resources. With current budget restrains, one may bring up treatment of rAAA and subsequent ICU admission in the elderly patient for discussion. Certainly, a balanced view between annual risk of rupture and natural live expectancy on one hand, and surgical risk and late-term survival on the other hand seems important. Also to this context, advanced age may be considered a factor to refrain from further treatment and ICU admission. The purpose of this study was to investigate whether this holds true for octogenarians suffering AAAA.

Materials and methods

Design of the study

Between January 2000 and February 2008, a total of 290 consecutive patients with manifest acute abdominal aortic aneurysm (AAAA) were presented at our hospital. Four patients died at our emergency room before surgery could be initiated. Fifteen patients were excluded from surgical intervention due to the criteria mentioned in the preoperative management section. Of these 15 patients (nine men, six women), nine patients were not treated due to severe co morbidities, two patients refused treatment and four patients were to haemodynamically unstable). All died shortly after arrival at the hospital. The remaining 271 patients were admitted to and treated in our tertiary referral hospital and form the basis of this report. Six of the 271 patients died during the operation and were included in the final analysis to ensure an intention to treat protocol. Data were prospectively entered into a vascular registry and analyzed retrospectively.

Preoperative management

At the regional level, we have an integrated system for the rapid transport and immediate treatment of AAAA. Our strategy was to treat all patients unless they had a very poor performance score (Karnofsky performance score ≤ 40). As such, 95% receives treatment. Further details regarding transport and early management have been described previously.[6] In short, for those transferred from another hospital, median transport time (from initial telephone call for ambulance transport to the first hospital to patient arrival at our hospital) was 40 minutes. Patients were only volume resuscitated in case of hemorrhagic shock with an altered mental state, regardless of actual blood pressure values. Furthermore, patients were almost never intubated before or during transport, as induction of anaesthesia interacts with the sympathic stimulus to maintain the blood pressure, often leading to a rapid decrease in blood pressure. Exclusion criteria for surgery were prolonged cardiac arrest despite resuscitation, advanced Alzheimer's disease and a poor Karnofsky performance score (≤ 40; i.e., the patient is disabled and requires special care and help), or severe cardiovascular disease associated with a New York Health Association-IV performance score. If information was incomplete, the patient was still offered surgery, regardless his/her age. Also, if the patient denied surgery after being extensively informed, no surgical intervention was performed.

Upon admission at the emergency department, evaluation of each patient was done simultaneously by a certified vascular surgeon, an anaesthesiologist, and an interventional radiologist, who were all called in even before the patient arrived to the hospital. At the same time the operating room was alerted. On arrival, the presumed diagnosis was verified by physical examination and duplex ultrasound. When ultrasound excluded (A)AAA (aortic diameter within normal range, no free intra-abdominal fluid) the patient received further examination and testing. If feasible a computerized tomography (CT) scan was immediately performed to further confirm the diagnosis and to evaluate suitability for endovascular repair (endovascular aneurysm repair [EVAR]). Until aortic clamping or balloon occlusion in the operating room, low systolic blood pressure was accepted as long as the patient remained conscious with coherent verbal responses. Patients who arrested during transport or in the emergency room, but were successfully resuscitated were offered open repair and included in the study. The consideration and arguments leading to either one of the treatment modalities have been described before.[5,7] In short, the multidisciplinary team on-call decided, based on hemodynamic status as well as the CT-images, whether the patient was suitable for EVAR (proximal neck length ≥ 15mm with < 60° angulation and access vessels ≥ 7mm) or open treatment.

Any intervention was performed by at least one certified vascular surgeon. For those who underwent open repair, a rapid sequence induction of anaesthesia and intubation was performed. A midline laparotomy was performed. After proximal and distal clamping, the aneurysm was opened and lumbar arteries were ligated. Reconstruction was conducted by placing either a Dacron aortic tube or aorto-iliac bifurcated graft. After surgery all patients remained intubated and mechanically ventilated and were transferred to our tertiary ICU.

Patients suitable for endovascular repair were preferably treated under local anaesthesia, which included approximately 85% of all patients who underwent endovascular repair for AAAA.

Study cohort

A total of 271 patients were analysed. There were 234 men and 37 women with a mean age of 72 ± s.d. 7.8 years (range 54-88). Seventeen percent of the patients was 80 years or older (N=46). Sixty patients who underwent endovascular repair were not admitted to the ICU and therefore no APACHE score could be calculated. From 35 patients no reliable APACHE II could be calculated due to missing data. For the remaining 176 patients the mean APACHE II score was 17 ± 7 (range 4-36). Open treatment was performed in 196 patients (72%) and endovascular treatment in 75 (28%). When divided in a younger (<80 years) and an older (≥80 years) group, no differences were observed, except for more women in the older group (Table 1).

Table 1. Patient characteristics

Parameter	Number or mean ± SD[a] (percentage or range)
Number of patients	271
Mean age (years)	72 ± 7.8 (54-88)
Age < 80 years	225 (83%)
Age ≥ 80 years	46 (17%)
Sex	
men	234 (86%)
women	37 (14%)
Open treatment	196 (72%)
Endovascular treatment	75 (28%)
APACHE II [b]	17 ± 6 (4-36)
Follow-up (months)	33 ± 30 (0-98)

[a] *Standard deviation*

[b] *APACHE II: Acute Physiology and Chronic Health Evaluation. Mean APACHE II score calculated from a total of 176 patients. 54 patients, all treated with an endovascular stent graft, were never admitted to the ICU. From 35 patients no reliable APACHE II could be calculated due to incomplete data.*

Definitions and outcome measures

Acute AAA was defined as either acute non-ruptured (N=82) or ruptured (CT or laparotomy-proven, N=189). The rAAA classification was only awarded in the presence of a retroperitoneal hematoma on CT or when clearly visible as a retroperitoneal haematoma during laparotomy. All other AAAAs were classified as symptomatic aneurysms (sAAA) as determined by acute onset of abdominal or back pain combined with pain at aneurysm palpation. Primary outcome measures were hospital and long-term mortality. Secondary outcome measures included ICU- and hospital length of stay and morbidity. Morbidity was specifically added to our analysis in order to assess quality of life in octogenarians.

Statistical analysis

Survival rates were calculated by means of Kaplan-Meier analysis. Differences in survival were determined using log-rank testing. Primary endpoint was any-cause mortality. Differences between categorical variables were tested with Pearson's χ^2 test (2 variables) or Kruskal-Wallis test (> 2 variables). Differences between means were tested with Student's two-tailed test (normal distribution) or Mann-Whitney U test (skewed distribution). Significance was set at $P < .05$. Data are presented as means (SD), unless stated otherwise. All statistical analyses were done with the Statistical Package for the Social Sciences (SPSS 16.0.1, SPSS; Chicago, ILL, USA, 2007).

Results

Early outcome

Mean ICU length of stay of all patients was 6.7 ± 11.0 days. The elderly patients did not tend to stay longer at the ICU, as mean ICU length of stay was 6.9 ± 11.5 days for patients younger than 80 and 5.7 ± 7.8 days for patients older than 80 years of age (P=.33). The same accounts for duration of hospital stay. Mean hospital length of stay of all patients was 16.4 ± 19.8 days. Again with a cut-off at the age of 80 years, mean hospital length of stay was 16.9 ± 20.4 days for patients younger than 80 and 13.7 ± 16.7 days for patients older than 80 years of age (P=.11) (Table 2).

Fifty-eight patients (21%) died during postoperative ICU and hospital stay. Mean age of these 58 patients was 75.8 ± 6.8 years; Twelve of 42 (28%) were 80 years of age or older and 40 of 223 (18%) were younger than 80 years. Mean age of patients who survived during ICU and hospital stay was 70.9 ± 7.8 years.

Table 2. Early and late procedure- and disease related outcomes; stratification by age.

Outcome[a]	Mean	Age < 80 years (percentage or range)	Age ≥ 80 years (percentage or range)	P value [b]
ICU length of stay (days)	6.7 ± 11 (0-98)	6.9 ± 11.5 (0-98)	5.7 ± 7.8 (0-30)	.33
Hospital length of stay (days)	16.4 ± 19.8 (0-134)	16.9 ± 20.4 (0-134)	13.7 ± 16.7 (0-75)	.11
In-hospital mortality[c]	58 (21%)	42 (19%)	16 (35%)	.02
Overall mortality[d]	105 (39%)	79 (35%)	26 (56%)	.007

[a] *Results presented as number or mean ± SD (Standard deviation) (< 80 years, N= 225, ≥ 80 years, N=46)*

[b] *P-values < 0.05 were considered a significant difference (tested with Pearson's χ^2 test (2 variables)*

[c] *Defined as mortality during postoperative ICU and hospital stay*

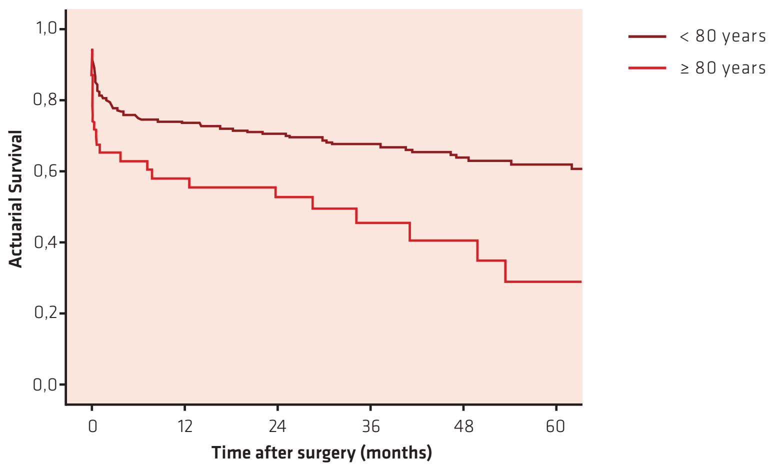
[d] *After mean follow-up (33 ± 30.4)*

Late outcome - mortality

The mean follow-up was 33 ± 30.4 months (including early deaths). During follow-up, 79 out of 225 patients younger than 80 years of age died, whereas 26 out of 46 patients older than 80 years died, including those already mentioned in the early outcome section ($P < .05$). As expected, a higher APACHE II score was significantly associated with a diminished survival (log rank test, $P < .001$). However, APACHE II scores did not differ between younger and older patients ($P = .36$). One-year actuarial survival for all patients was 71%. After two and five years, these numbers were 67% and 57%, respectively. Kaplan Meier survival analysis revealed a significantly better survival for the younger patients ($P < .05$) (Fig 1). Stratification based on urgency (rAAA vs. sAAA) or treatment (EVAR vs. open repair) did not change the difference (Figs 2 and 3). Furthermore, 18 out of 75 patients (24%) who underwent endovascular repair died during follow-up, compared to 87 out of 196 patients (44%) in the open repair group ($P < .05$). Two-year actuarial survival was 70% for patients younger than 80 and 52% for those older than 80. At five years follow-up, these figures were 62% and 29%, respectively. Mean survival in patients younger than 80 was 64.5 ± 3.0 months versus 39.8 ± 6.8 months in those older than 80. The overall mortality for sAAA was 29 % (21 of 73) for patients younger than 80 and 44% (4 of 9) for patients older than 80 years ($P = .34$). Overall mortality for rAAA was 37% (58 of 152) for patients younger than 80 and 55% (22 of 37) for patients older than 80 years ($P = .02$).

Figure 1.

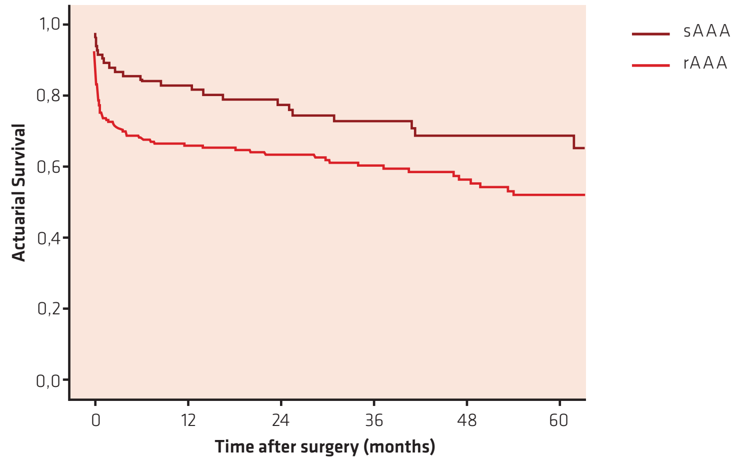
Probability of patient survival according to the Kaplan-Meier method following repair of acute abdominal aortic aneurysm; comparison of patients younger than 80 years of age and those being 80 years or older. There is a significantly better survival for the younger patients (log rank test $P < .05$).



No. at risk	0	12	24	36	48	60
< 80 years	225	152	130	100	74	59
≥ 80 years	46	24	19	12	7	3

Figure 2.

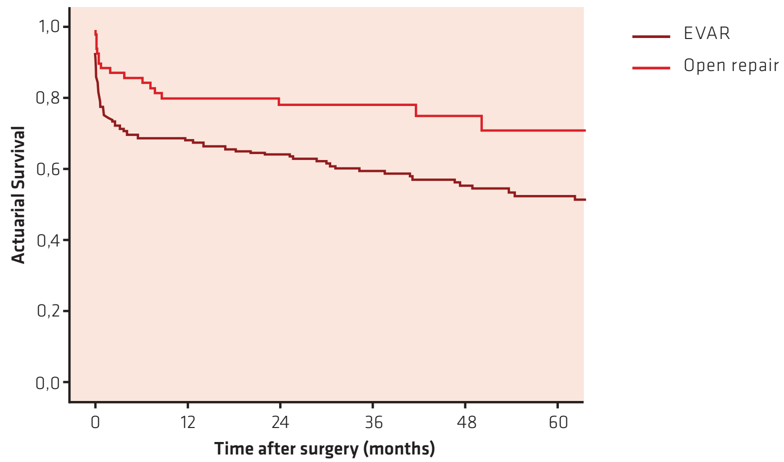
Probability of patient survival according to the Kaplan-Meier method following repair of acute abdominal aortic aneurysm; comparison of patients with a symptomatic aneurysm (sAAA) or ruptured aneurysm (rAAA). There is a significantly better survival after sAAA (log rank test $P < .05$).



No. at risk	0	12	24	36	48	60
sAAA	82	64	53	40	28	21
rAAA	189	112	96	72	53	41

Figure 3.

Probability of patient survival according to the Kaplan-Meier method following repair of acute abdominal aortic aneurysm; comparison of patients after endovascular aneurysm repair (EVAR) or open repair. There is a significantly better survival for the EVAR patients (log rank test $P < .05$).



No. at risk	0	12	24	36	48	60
EVAR	75	52	45	31	18	12
Open repair	196	124	104	81	63	50

Late outcome - morbidity

Twenty-five patients (9%) developed lower leg peripheral thromboembolism which was treated by surgical trombectomy in 22 patients. Three patients were considered unsuitable for redo-surgery due to severe concurrent multi-organ failure and died. These numbers were included in the above mentioned actuarial survival rates. One patient (0.4%) underwent an above the knee amputation. Renal insufficiency, defined as needing renal replacement therapy, was divided into temporary and chronic renal failure. Eight patients (3%) developed temporary renal failure whereas four patients (1.5%) required chronic or permanent dialysis. Twelve patients died with renal failure, mostly due to multiple organ failure. Another severe, disease-related complication after surgery was colonic ischemia which arose in 28 patients (10%). Twenty-four patients underwent surgery, with resection of the affected colonic segment and colostomy, and four patients died. In 92% of the patients the colostomy was permanent (Table 3). Mortality due to multiple organ failure, renal insufficiency or colonic ischemia was also included in the actuarial survival rates mentioned in the late outcome-mortality section. No statistical differences were observed in the above mentioned complications between the younger (< 80 years of age) and older (≥ 80 years of age) group (Table 3). As expected, there was a significant difference, in most procedure- and disease related complications, as well as ICU and hospital length of stay, in favour of sAAAs (Table 4 and 5).

Table 3. Disease-related complications: Stratification based on age.

Complication	Total (%)	Age < 80 years (%)	Age ≥ 80 years (%)	P value [a]
Peripheral emboli	25 (9)	20 (75)	5 (25)	.91
Intervention [b]	22 (8)	18 (82)	4 (18)	.25
No intervention	3 (1)	2 (67)	1 (33)	.54
Amputation	1 (0.4)	1 (100)	0 (0)	.66
Renal failure [c]	24 (9)	22 (92)	2 (8)	.27
Temporary	8 (3)	8 (100)	0 (0)	.42
Chronic	4 (2)	3 (75)	1 (25)	.54
Died with renal failure	12 (5)	9 (75)	3 (25)	.43
Colonic ischemia [d]	28 (11)	22 (78)	6 (22)	.29
Requiring surgery	24 (9)	19 (79)	5 (21)	.48
Permanent stoma	22 (8)	17 (77)	5 (33)	.48
Graft infection	2 (1)	2 (100)	0 (0)	.54

[a] *P-values < 0.05 were considered a significant difference (tested with Pearson's χ^2 test (2 variables)*

[b] *Surgical trombectomy*

[c] *Requiring dialysis*

[d] *Requiring surgical resection with colostomy (Hartmann's procedure)*

Table 4. Disease-related complications: Stratification based on urgency.

Complication	sAAA[a]	rAAA[b]	P value[c]
Peripheral emboli	3 (4%)	21 (11%)	.05
Renal failure [d]	4 (5%)	20 (11%)	.13
Colonic ischemia [e]	1 (1%)	23 (12%)	.004
Graft infection	0 (0%)	2 (1%)	.35
Death	25 (30%)	80 (39%)	.06

[a] *Symptomatic (non-ruptured) abdominal aortic aneurysm (N=82)*

[b] *Ruptured or symptomatic abdominal aortic aneurysm (N=189)*

[c] *P-values < 0.05 were considered a significant difference (tested with Pearson's χ^2 test (2 variables)*

[d] *Requiring dialysis*

[e] *Requiring surgical resection with colostomy (Hartmann's procedure)*

Discussion

This study shows that our strategy of treating octogenarians with AAAA was associated with satisfactory short- and long-term outcome. Furthermore, the disease related morbidity seems very acceptable with no statistical difference between the younger and older patients. Remarkably, octogenarians had a similar duration of hospital- as well as ICU length of stay compared to younger (< 80 years) patients. Our two- and five-year actuarial survival results are consistent with the literature.[6-11] Whereas most studies concentrate on survival rate, we also focused on morbidity with similar good results in this already highly vulnerable group. From different studies, focusing on outcome after abdominal surgery in the elderly, we know that the hospital mortality can be as high as 15-26%.[12,13]

Table 5. Early and late procedure- and disease related outcomes; stratification by urgency (symptomatic vs. ruptured aneurysm).

Outcome[a]	Mean (percentage or range)	sAAA (percentage or range)	rAAA (percentage or range)	P value [b]
ICU length of stay (days)	6.7 ± 11 (0-98)	2.6 ± 3.2 (0-13)	8.5 ± 12.5 (0-98)	.0001
Hospital length of stay (days)	16.4 ± 19.8 (0-134)	11.2 ± 9.9 (0-54)	18.7 ± 22.5 (0-134)	.02
In-hospital mortality [c]	58 (21%)	7 (8%)	49 (26%)	.001
Overall mortality [d]	105 (39%)	25 (30%)	80 (42%)	.06

[a] *Results presented as number or mean ± SD (Standard deviation) (sAAA, N=82, rAAA, N=189)*

[b] *P-values < 0.05 were considered a significant difference (tested with Pearson's χ^2 test (2 variables) or Mann-Whitney U test (skewed distribution))*

[c] *Defined as mortality during postoperative ICU and hospital stay*

[d] *After mean follow-up (33 ± 30.4)*

Although age and most age-related co-morbidities as renal dysfunction and cardiopulmonary disease are repeatedly mentioned as negative predictive factors for survival, the outcome seems far less dismal than reported and suggested in the literature.[14,15] Even though the survival rates for octogenarians are less favourable compared to a younger group, still a mean of 3.3 more life years (median 2.4 years) can be gained with a relatively low morbidity. With a mean survival for octogenarians in the Dutch population (matched for both age and sex) of 6.05 years (median 3.92 years), there is clearly much to gain.[16] Recent studies assessing the outcome of critically ill elderly patients at the ICU found not only that high age alone is no longer a reason to refuse intensive care admission, but also, over the past decade; an improvement in survival is noticed.[17,18] This does suggest that our previous understanding of determining who is fit enough for elective AAA repair, and who could potentially benefit from it, should also be reconsidered.

There are, however, several drawbacks in this study that need to be addressed. Patients who arrived alive at the hospital but denied surgery or were excluded due to the criteria mentioned in the preoperative management section (N=15) were excluded from further analysis. Although we did use an intention to treat analysis for patients who arrived at the operating room, there may still be some sort of selection bias. However, in view of the main objective of our study, there was an equal distribution in age (< 80 years 7 patients and ≥ 80 years 8 patients). Also, this was a retrospective cohort study and no randomisation was performed. However, with a natural course resulting in death, in case of rAAA, a study design with randomisation is unethical. Also, a quality of life (QoL) assessment was not part of this study. However, when assuming that QoL is (partially) determined by complications interfering with the activities of daily living, our procedure- and disease-related complications are low and comparable both with the literature as well as with a younger population.[19] In our population, one patient (0.4%) underwent an amputation of a lower extremity. This patient died two months after surgery due to an infected graft. Four patients (1.5%) needed permanent haemodialysis of which three patients died during follow-up, all of a non-aneurysm related cause. Nevertheless, these factors must be taken into account when assessing these patients for surgery. Unlike primary outcome measures such as survival and procedure-related morbidity, functional outcome should be considered as well. Even the effect of a procedure related event such as a lower leg amputation can be disastrous. In a heterogenic population only 40% of patients who underwent amputation of a lower extremity regain full mobility and 30% is dead after two years.[20] If survival after rAAA is followed by permanent disability and long-term care institutionalisation, the benefit would clearly become less apparent. However, these arguments do not apply on our population of ruptured or symptomatic aneurysms needing emergency surgery. But in an elective setting these numbers seem far more relevant. Furthermore, constant improvements in both surgical techniques as postoperative ICU care probably have contributed to our results and will do so in the near future with further development of endovascular techniques. And with the increasing use of endovascular procedures in octogenarians reported in the literature, this will probably further contribute to lowering the procedure related morbidity and mortality. Although not a primary focus of this study we did find a significantly lower mortality rate and reduced ICU and hospital length of stay in the EVAR group (Table 6). Even though endovascular repair is associated with a higher incidence of reinterventions and without the benefit of reducing all-cause mortality, it is still associated with a significant reduction in post-operative complications.[21] This, of course, is an advantage which fits well with an already high risk population such as octogenarians. Several studies do confirm this idea and found good results after endovascular repair with a lower early mortality in octogenarians.[22-26] With an already limited life expectancy the benefit of reducing post-operative morbidity and mid-term mortality seems specifically applicable to this group.

Table 6. Early and late procedure- and disease related outcomes; stratification by type of treatment (endovascular vs. open repair).

Outcome[a]	Mean (percentage or range)	EVAR (percentage or range)	Open repair (percentage or range)	P value [b]
ICU length of stay (days)	6.7 ± 11 (0-98)	2.2 ± 4.7 (0-22)	8.5 ± 12.1 (0-98)	.0001
Hospital length of stay (days)	16.4 ± 19.8 (0-134)	10.6 ± 17.4 (0-134)	18.6 ± 20.3 (0-105)	.0001
In-hospital mortality [c]	56 (21%)	9 (12 %)	47 (25%)	.03
Overall mortality [d]	105 (39%)	18 (24%)	87 (44%)	.002

[a] *Results presented as number or mean ± SD (Standard deviation) (EVAR, N=79, open repair, N=196)*

[b] *P-values < 0.05 were considered a significant difference (tested with Pearson's χ^2 test (2 variables) or Mann-Whitney U test (skewed distribution))*

[c] *Defined as mortality during postoperative ICU and hospital stay*

[d] *After mean follow-up (33 ± 30.4)*

Conclusions

In conclusion, even with a devastating event such as rAAA and sAAA, a median survival of more than 2.8 years can be achieved in octogenarians, while ICU and hospital length of stay is not prolonged compared to younger patients, with certain death without treatment. Also, there is no statistical difference in disease-related complications between a younger (< 80 years of age) and older (≥ 80 years of age) group. Assuming an integrated system for managing AAA is in place, advanced age is not a reason to deny patients surgery.

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CHAPER 3

ENDOVASCULAR ABDOMINAL AORTIC ANEURYSM REPAIR IN OCTOGENARIANS: EARLY OUTCOME AND QUALITY OF LIFE FROM THE ENDURANT STENT GRAFT NATURAL SELECTION GLOBAL POST-MARKET REGISTRY (ENGAGE)

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ABSTRACT

Objective

To determine 30-day outcome and quality of life after elective endovascular abdominal aortic aneurysm repair in octogenarians.

Materials and Methods

From March 2009 until May 2011, 1200 patients with abdominal aortic aneurysms were treated with endovascular aneurysm repair (EVAR) using the Endurant stent graft were included in the Endurant Stent Graft Natural Selection Global Postmaket Registry (ENGAGE). Among these, 926 (77%) were aged < 80 years and 274 (23%) were aged ≥ 80 years. Quality of life was assessed using composite EuroQol 5-Dimensions Questionnaire index scores.

Results

Gender was unequally distributed with more female patients among the octogenarians (P= .043). Octogenarians had a significantly higher American Society of Anaesthesiologists classification (P< .001) and differed significantly in baseline risk factors. The younger cohort was more likely to smoke (P< .001) and be alcoholics (P= .005). Octogenarians had larger aortic aneurysms (P= .01) and left iliac artery diameters (P= .017) and greater infrarenal neck angulation (P= .01). The technical success rate was > 99% for both cohorts. Octogenarians were more often operated on under general anaesthesia (P=.028), had a longer procedure duration (P= .001), greater peril-procedural blood loss (P=.05), and an increased length of hospitalization; both total (P< .001) and post-procedure (P< .001). All-cause mortality and major adverse event rates were similar in the two groups (P= .835 and P= .186, respectively). There was no difference in the number of secondary endovascular procedures or aneurysm rupture at 30-days.

Conclusions

Octogenarians can be safely treated using the Endurant stent graft with a high technical rate of success, low perioperative mortality, and no reduction in quality of life. Octogenarians did, however, appear to recover more slowly than younger patients with respect to certain quality of life components. Long-term data are needed to confirm these results.

Introduction

There is a steady increase in life expectancy in industrialized countries. As abdominal aortic aneurysm (AAA) is an age-related disease, more elderly patients, including octo- and even nonagenarians, will be referred for AAA management. Because open AAA repair in these age groups is associated with high morbidity and mortality rates, endovascular repair (EVAR) could potentially offer substantial benefit. A systematic review of elective treatment of AAAs in octogenarians has demonstrated acceptable survival rates with a perioperative mortality rate after open repair of approximately 7.5% (95% confidence interval [CI] 6.1-9.0) and a 5-year survival rate of 60%.[1] In the group treated by EVAR, the perioperative mortality rate was 4.6% (95% CI 3.5-6.0). Long-term survival rates in both groups were also acceptable, but small sample size, selection, and publication bias had to be taken into account. Although the goal of AAA repair is to prevent rupture, the risk of rupture in this group with a limited life expectancy must be balanced against the risk of the procedure. Further, one must consider effects on quality of life. Even if mortality rates are acceptable, decrements in such issues as mobility and self-care must be considered. The threshold age of 80 years seems a good cut-off point for analysis because, although arbitrary, current literature has used this cut-off in binary analyses.[2-6]

The Endurant Stent Graft Natural Selection Global Postmarket Registry (ENGAGE) is a multicenter, noninterventional, nonrandomized, single-arm prospective study of the Endurant stent graft device (Medtronic Cardiovascular, Santa Rosa, California, USA). These data provide a large database to test the hypothesis that octogenarians may be safely treated with EVAR while still providing acceptable post-procedure quality of life.

Materials and methods

The study population included consecutive patients enrolled in the ENGAGE registry from 80 sites in Western, Central and Eastern Europe, Asia, South Africa, Middle East, Latin America and Canada. The patients were divided in two groups; those aged > 80 years (274, 22.8%) and those ≤ 80 years (926, 71.2%). Information on study design, the Endurant stent graft system, data collection, monitoring and statistical methods has been published previously[7]. In short, patients were enrolled in the registry on an intention-to-treat manner. Protocol-defined inclusion criteria included age ≥18 years or minimum age as required by local regulations and indication for elective surgical repair of AAA with an endovascular stent graft in accordance with the applicable guidelines on endovascular interventions and the instructions for use for the Endurant stent graft system.[8] A signed consent form was obtained from all patients. Patients were excluded if they had a high probability of non-adherence to physician's follow-up requirements or when they were participating in a concurrent trial that could confound the study results. The study is registered on http://clinicaltrials.gov (NCT00870051).

Study data was recorded by the participating hospitals on electronic case forms. Preoperative risk assessment consisted of American Society of Anaesthesiologists (ASA) classification and Society of Vascular Surgery/International Society of Vascular Specialists (SVS) scores. Baseline comorbidities (hypertension, hyperlipidaemia, diabetes, cancer, cardiac disease, tobacco use, renal insufficiency) and anatomic characteristics of the aneurysm (aneurysm diameter, length of non-aneurysmal neck, proximal and distal neck diameter, iliac artery diameters and infrarenal neck angle) were tabulated. Perioperative outcome data included technical success of stent-graft placement (defined by successful introduction of the delivery system and deployment of the device), freedom from intraoperative death, or type I/III endoleak. A successful implantation was defined in the absence of stent kinking or twisting, suprarenal bare stent fracture, or stentgraft malfunction (including type I or IV endoleak). Measures assessed after discharge included freedom from migration, graft occlusion, loss of structural integrity, endoleak, aneurysm expansion, major adverse device-related effects, and all-cause mortality.

Quality of life was assessed using the EuroQoL 5 -Dimensions Questionnaire (EQ-5D) index score; a preference-based, generic instrument that measures quality of life in three different ways.[9,10] The first part was a descriptive system profiling a respondents' health status in five dimensions; mobility, self-care, usual activities, pain/discomfort and anxiety/depression, on a scale of 1-3 ranging from no problems to extreme problems. The second measure was a 0 to 100 visual analogue scale for self-rating of a patient's own health. The last measure reflected the utility of the measured health profile from the perspective of the general population, termed the "composite EQ-5D index". Ratings took place at the first contact (baseline), at discharge, and at the 30-day outpatient visit. Differences were measured at baseline, discharge, and at 30 days, comparing values between groups at each time point and within groups between baseline and each of the two postoperative time points.

Statistical analysis

Differences between continuous variables were tested with Student's two-tailed test except for hospital stay, procedural stay, and intensive care unit (ICU) time, where Wilcoxon rank sum test was applied. Normally distributed continuous variables are expressed as mean ± standard deviation, while skewed variables are expressed as median and interquartile range. For categorical data, the Cochran-Mantel-Haenzel test was used. Within-group change from baseline in each EQ-5D dimension was tested using the Stuart-Maxwell test. Two-tailed P-values were used throughout, and significance was assumed when the P value was < .05. All statistical analyses were performed with SAS statistical software (SAS institute, Carey, NC)

Results

Baseline characteristics

From March 2009 until May 201,1 1200 patients with infrarenal AAA were enrolled in the ENGAGE registry and treated with an Endurant stent graft. The baseline characteristics are shown in Table 1. The mean age was 70.1 ± 6.5 in the 926 patients aged 80 and below, and 83.3 ± 2.9 years in the 274 older patients. Gender was unequally distributed with more female patients among the octogenarians (P= .043). The primary indication for stent graft placement was similar in both groups. Octogenarians had a significantly higher ASA classification (P < .001), whereas the younger cohort was more likely to smoke (P < .001) and consume alcohol (P= .005). As expected, octogenarians differed significantly in the occurrence of age-dependent risk factors, with an increased incidence of renal insufficiency and cerebrovascular/neurological disease. Interestingly, cardiac status and pulmonary status were evenly distributed between the two groups.

Table 1: Baseline characteristics, risk factors and comorbidity.

Baseline Characteristics	**Age < 80 years (N=926)**	**Age ≥ 80 years (N=274)**	**P value**
Age	70.1 ± 6.5	83.3 ± 2.9	NA
Gender			.043
Female	9.3% (86/926)	13.5% (37/274)	
Male	90.7% (840/926)	86.5% (237/274)	
Primary indication for implant			.029
Aneurysm diameter			
>=1.5x normal infrarenal aorta	3.0% (28/926)	2.6% (7/274)	
4-5 cm (>=0.5 cm increase in last 6 months)	7.6% (70/926)	2.9% (8/274)	
>5 cm	86.9% (805/926)	93.1% (255/274)	
Other	2.5% (23/926)	1.5% (4/274)	
Baseline symptoms			
None	84.0% (778/926)	86.5% (237/274)	.318
Abdominal pain	9.9% (92/926)	9.5% (26/274)	.828
Back pain	6.0% (56/926)	3.3% (9/274)	.076
Other	2.5% (23/926)	2.9% (8/274)	.690
Risk factors			
Tobacco use	56.1% (508/905)	24.6% (65/264)	< .001
Hypertension	76.6% (699/912)	73.1% (198/271)	.227
Hyperlipidaemia	64.1% (560/874)	55.1% (140/254)	.010
Diabetes mellitus	20.3% (185/912)	15.1% (41/271)	.058
Cancer	19.5% (178/913)	22.5% (60/267)	.287
Alcoholism	3.7% (33/901)	0.4% (1/266)	.005
Cardiac disease	53.8% (498/925)	55.5% (152/274)	.633
Pulmonary disease	25.4% (231/908)	25.5% (69/271)	.995
Renal insufficiency	14.2% (130/916)	20.1% (55/273)	.017
Carotid artery disease	10.7% (82/767)	12.0% (28/233)	.571
Cerebrovascular/neurological disease	12.0% (111/925)	16.8% (46/274)	.039
Vascular disease	32.0% (296/925)	31.0% (85/274)	.760
ASA classification			< .001
Class I	6.0% (55/924)	1.8% (5/273)	
Class II	44.0% (407/924)	35.9% (98/273)	
Class III	39.7% (367/924)	48.7% (133/273)	
Class IV	10.3% (95/924)	13.6% (37/273)	
SVS/ICVS Risk Level			NA
SVS 0	0.1% (1/888)	0.0% (0/267)	
SVS 1	17.5% (155/888)	0.0% (0/267)	
SVS 2	66.7% (592/888)	0.0% (0/267)	
SVS 3	15.8% (140/888)	100.0% (267/267)	

NA=not applicable
Data are presented as means ± standard deviation or percentage, unless stated otherwise.
P-values ≤ 0.05 were considered statistically significant
n = number of ITT subjects with non-missing values. One subject can report more than one baseline symptom; hence, sum of all the counts can be more than the denominator.
ASA= American Society of Anaesthesiologists classification
SVS/ISVS= Society of Vascular Surgery/International Society of Vascular Specialists risk scores

Anatomic characteristics

Anatomic details are shown in Table 2. Octogenarians had a significantly larger aneurysms (62.0±11.7 vs. 59.9±11.6 mm, P= .010) greater infrarenal neck angulation (33.5±24.2 vs. 29.2±23.8, P= .010) and significantly larger left iliac arteries (14.3±3.6 vs. 13.6±3.6, P= .017).

Table 2. Anatomical details

Aneurysm measurements	**Age < 80 years (N=926)**	**Age ≥ 80 years (N=274)**	**P value**
Maximum diameter of aneurysm (mm)	59.9 ± 11.6	62.0 ± 11.7	.010
Proximal neck diameter (mm)	23.8 ± 3.6	23.8 ± 3.6	.965
Distal neck diameter (mm)	24.9 ± 4.1	24.9 ± 3.9	.952
Length of non-aneurysmal aortic neck (mm)	27.0 ± 12.5	27.5 ± 12.4	.625
Distal diameter of non-aneurysmal neck of right iliac artery (mm)	14.2 ± 4.0	14.5 ± 3.7	.201
Distal diameter of non-aneurysmal neck of left iliac artery (mm)	13.6 ± 3.6	14.3 ± 3.6	.017
Infrarenal neck angle (°)	29.2 ± 23.8	33.5 ± 24.4	.010

Data are presented as means ± standard deviation, unless stated otherwise.
P-values ≤ 0.05 were considered statistically significant.

Initial procedural data and hospital stay

There are some interesting statistical differences between the procedural data of the two cohorts. General anesthesia was employed more often in octogenarians (p= .028). The duration of implant procedure was significantly higher in the elderly cohort (P= .001) which may have contributed to a longer hospital (P< .001) and post-procedure stay (P< .001). The technical success rate was equal in both groups (Table 3). The 30-day all-cause mortality was comparable between the two groups with 12 deaths (1.3%) in the cohort aged ≤ 80 years and 4 deaths (1.5%) among the octogenarians (P= .119). There was no significant difference in major adverse events between the two roups (P= .186). However, higher incidence of myocardial infarction (2.6% vs. 0.8%, P= .015) and procedural blood loss of 1000 mL or more (2.6% vs. 1.2%, P= .102), were observed in the octogenarians group (Table 4). After 30 days, there was no difference in the number of secondary endovascular procedures or aneurysm rupture. Although there was a slightly higher incidence of conversion to open surgery in the elderly group (0.4% vs. 0%), this did not reach statistical significance (Table 5). Except for a higher incidence of graft twisting (P= .01), there were no differences in the rate of kinking, stent fracture, or other malfunctions up to 30 days of follow-up. There was, however, a significantly higher incidence of type I endoleak in the octogenarian group (P< .001) (Table 6).

Table 3. Initial procedural data and hospital stay

Measurement	Age < 80 years (N=926)	Age ≥ 80 years (N=274)	P value
Type of anaesthesia			
General	60.8% (563/926)	68.1% (186/273)	.028
Spinal	22.8% (211/926)	19.0% (52/273)	.190
Epidural	8.7% (81/926)	6.6% (18/273)	.256
Local	12.7% (118/926)	10.3% (28/273)	.270
Duration of implant procedure (mins)	97.7 ± 45.3	107.8 ± 42.8	.001
Estimated blood loss during procedure (cc)	203.4 ± 214.3	233.9 ± 246.6	.049
Evaluation of Endurant			
Endurant stent graft successfully delivered	99.4% (920/926)	99.6% (273/274)	.589
Endurant stent graft successfully deployed	99.4% (920/926)	99.6% (273/274)	.589
Total hospital stay (days)	6.03 ± 6.44	7.33 ± 6.00	<.0001
Post-procedure stay (days)	4.49 ± 4.90	5.66 ± 5.49	<.0001
Duration of intensive care unit stay (hours)	10.8 ± 48.7	8.0 ± 17.3	.854
Intra-operative clinical success	97.5% (903/926)	98.2% (269/274)	.526
Technical success	99.0% (917/926)	99.3% (272/274)	.712
Freedom from intra-operative death	100.0% (926/926)	100.0% (274/274)	
Freedom from type I/III endoleak (uncorrected)	98.5% (907/921)	98.9% (270/273)	.606

Data are presented as means ± standard deviation, unless stated otherwise.
P-values ≤ 0.05 were considered statistically significant
Overall hospital stay (days) = Date of Hospital Discharge – Date of Hospital Admission. In the case where Date of Hospital Discharge = Date of Hospital Admission, Overall hospital stay will be considered to be 0.5 day.
Procedural hospital stay (days) = Date of Hospital Discharge - Date of Initial Procedure. In the case where Date of Hospital Discharge = Date of Initial Procedure, procedural hospital stay will be considered to be 0.5 day

Table 4. Early outcome

Event	Age < 80 years (N=926)	Age ≥ 80 years (N=274)	P value
All-cause mortality	1.3% (12/926)	1.5% (4/274)	.835
One or more major adverse events (MAE)	3.7% (34/926)	5.5% (15/274)	.186
All-cause Mortality	1.3% (12/926)	1.5% (4/274)	
Bowel ischemia	0.2% (2/926)	0.4% (1/274)	
Myocardial infarction	0.8% (7/926)	2.6% (7/274)	
Paraplegia	0.0% (0/926)	0.0% (0/274)	
Procedural blood loss >= 1000 cc	1.2% (11/926)	2.6% (7/274)	
Renal failure	0.4% (4/926)	0.0% (0/274)	
Respiratory failure	0.0% (0/926)	0.0% (0/274)	
Stroke	0.1% (1/926)	0.4% (1/274)	
Intra-operative			
Conversion to open surgery	0.2% (2/926)	0.0% (0/274)	.442
Aneurysm rupture	0.1% (1/926)	0.0% (0/274)	.586
Secondary endovascular procedure	0.0% (0/926)	0.4% (1/274)	.066
Secondary endovascular procedure to correct type I/III endoleak	0.0% (0/926)	0.0% (0/274)	NA
1 - 30 Days			
Conversion to open surgery	0.0% (0/926)	0.4% (1/274)	.066
Aneurysm rupture	0.0% (0/926)	0.0% (0/274)	.586
Secondary endovascular procedure to correct type I/III endoleak	0.2% (2/926)	0.7% (2/274)	.195
Secondary endovascular procedure	1.5% (14/926)	1.5% (4/274)	.950

NA= not applicable
Data are presented as means ± standard deviation, unless stated otherwise.
P-values ≤ 0.05 were considered statistically significant

Quality of Life

Quality of life data are displayed in Table 6 for quality of life data between groups at each of the three time points (intergroup differences) and within each group from preoperative baseline to discharge and 30 days (intragroup differences). At the preoperative baseline assessment, quality of life was similar in the octogenarian and the younger patient group, both with respect to scoring of overall state of health (P= .980) and the composite EQ-5D index (P= .346). Dimensions of health status were also similar between the two groups with respect to the level of usual activities (P= .070), pain/discomfort (P= .692), and anxiety/depression (P= .228). Octogenarians, however, scored themselves lower than younger patients in the dimensions of baseline mobility (P= .046) and self-care (P< .001).

Table 5. Initial stent graft outcome

Measurement	Age < 80 years (N=921)	Age ≥ 80 years (N=273)	P value
Stent graft kinking	0.9% (8/919)	1.5% (4/272)	.384
Stent graft twisting	0.2% (2/918)	1.5% (4/272)	.010
Stent graft wire form fracture	0.0% (0/919)	0.0% (0/272)	NA
Suprarenal bare stent fracture	0.0% (0/919)	0.0% (0/272)	NA
Additional stent graft malfunction(s)	0.3% (3/921)	0.4% (1/273)	.919
Endoleak (Corrected)	7.3% (67/921)	14.7% (40/273)	< .001
Type I	4.6% (42/921)	12.1% (33/273)	< .001
Type II	2.0% (18/921)	2.2% (6/273)	.807
Type III	0.7% (6/921)	0.4% (1/273)	.589
Type IV	0.1% (1/921)	0.0% (0/273)	.586
Undetermined	0.1% (1/921)	0.4% (1/273)	.361
Endoleak (Uncorrected)	15.4% (142/921)	19.4% (53/273)	.117
Type I	1.1% (10/921)	1.1% (3/273)	.985
Type II	11.8% (109/921)	16.1% (44/273)	.064
Type III	0.4% (4/921)	0.0% (0/273)	.276
Type IV	1.4% (13/921)	2.6% (7/273)	.193
Undetermined	1.0% (9/921)	0.0% (0/273)	.101

NA=not applicable
Data are presented as means ± standard deviation or percentage, unless stated otherwise.
P-values ≤ 0.05 were considered statistically significant

At discharge, both groups scored themselves lower in all health status dimensions compared with their preoperative baseline, except for anxiety/depression which was improved over baseline in the younger group (P< .001) and similar to baseline in the octogenarians (P= .241). Compared with younger patients, octogenarians had decreased self-care perceptions at discharge (P= .041). The discharge health state and composite EQ-5D were not significantly different between the octogenarians and younger group (P= .093, P= .063, respectively), and did not differ between the two groups at the time of discharge from their baselines (P= .999, P= .500, respectively).

At 30 days after operation, recovery was seen in both age groups in mobility and pain/discomfort. However, both the octogenarians and younger group had persistent decreases in self-care (P= .029 and P= .011, respectively) and the usual activities (P= .003 and P= .004, respectively) dimension compared with preoperative baseline. The younger patients had lessened anxiety/depression (P< .001) vs. their baseline, while the octogenarian group did not display a similar level of improvement in this dimension (P= .746). Compared with younger patients, the octogenarians had a lower composite EQ-5D index (P= .003) and they scored themselves lower in the mobility (P< .001), usual-activities (P< .001) and self-care (P< .001) dimensions at 30 days when compared with the younger group. There were no significant intergroup differences despite in the 30-day overall health state (P= .090). There were no intragroup differences in the composite EQ-5D index between baseline and 30 days (P= .163), or between discharge and 30 days (P= .392) in either group.

Octogenarians scored their baseline state of health to be the same as the younger patients (P= .980), and small differences at discharge and 30 days did not attain statistical significance (P= .063 and P= .090, respectively). By contrast, the composite EQ-5D index, while similar in the two groups at baseline and at discharge, was significantly lower in octogenarians than younger patients at 30 days (P= .003). In summary, recovery of quality of life measured appeared to occur sooner in those patients below age 80.

Table 6. Outcome of activities of daily living and quality of life.

Event	Age < 80 years (N=926)	Age ≥ 80 years (N=273)	P value
Baseline			
Mobility			.046
1 (no problem)	70.8% (627/886)	63.6% (168/264)	
2 (some problems)	28.4% (252/886)	36.0% (95/264)	
3 (extreme problems)	0.8% (7/886)	0.4% (1/264)	
Self-care			< .001
1 (no problem)	92.9% (823/886)	84.1% (222/264)	
2 (some problems)	6.0% (53/886)	14.0% (37/264)	
3 (extreme problems)	1.1% (10/886)	1.9% (5/264)	
Usual activities			.070
1 (no problem)	81.9% (726/886)	76.1% (201/264)	
2 (some problems)	15.6% (138/886)	21.2% (56/264)	
3 (extreme problems)	2.5% (22/886)	2.7% (7/264)	
Pain/Discomfort			.692
1 (no problem)	65.8% (583/886)	64.0% (169/264)	
2 (some problems)	31.3% (277/886)	33.3% (88/264)	
3 (extreme problems)	2.9% (26/886)	2.7% (7/264)	
Anxiety/Depression			.228
1 (no problem)	72.5% (642/886)	75.8% (200/264)	
2 (some problems)	24.2% (214/886)	22.0% (58/264)	
3 (extreme problems)	3.4% (30/886)	2.3% (6/264)	
Your own health state today	72.8 ± 16.9	72.8 ± 16.4	.980
(0: bad to 100: excellent)			
Median (IQR)	75.0 (0.81-1.00)	75.0 (0.79, 1.00)	
EQ-5D Index	0.86 ± 0.17	0.85 ± 0.17	.346
Median (IQR)	0.85 (0.81-1.00)	0.84 (0.79-1.00)	
At discharge			
Mobility			.073
1 (no problem)	55.1% (425/772)	48.9% (110/225)	
2 (some problems)	43.4% (335/772)	48.4% (109/225)	
3 (extreme problems)	1.6% (12/772)	2.7% (6/225)	
Self-care			.041
1 (no problem)	76.3% (588/771)	71.6% (161/225)	
2 (some problems)	22.3% (172/771)	24.9% (56/225)	
3 (extreme problems)	1.4% (11/771)	3.6% (8/225)	
Usual activities			.062
1 (no problem)	61.7% (476/772)	52.9% (119/225)	
2 (some problems)	32.0% (247/772)	40.0% (90/225)	
3 (extreme problems)	6.3% (49/772)	7.1% (16/225)	
Pain/Discomfort			.385
1 (no problem)	46.0% (355/771)	42.7% (96/225)	
2 (some problems)	51.5% (397/771)	54.7% (123/225)	
3 (extreme problems)	2.5% (19/771)	2.7% (6/225)	
Anxiety/Depression			.739
1 (no problem)	80.9% (624/771)	80.4% (181/225)	
2 (some problems)	17.9% (138/771)	17.8% (40/225)	
3 (extreme problems)	1.2% (9/771)	1.8% (4/225)	
Your own health state today			
(0: bad to 100: excellent)	71.8 ± 15.9	69.7 ± 16.8	.093
Median (IQR)	70.0 (60-82)	70.0 (60-80)	
EQ-5D Index	0.81 ± 0.18	0.78 ± 0.18	.063
Median (IQR)	0.83 (0.74-1)	0.81 (0.71-86)	
Change from Baseline to Discharge	-0.05 ± 0.17	-0.06 ± 0.17	.500
Median (IQR)	0.00 (-0.16-0)	-0.01 (-0.17-0)	
After 30 days			
Mobility			< .001
1 (no problem)	68.4% (523/765)	54.3% (125/230)	
2 (some problems)	30.8% (236/765)	43.0% (99/230)	
3 (extreme problems)	0.8% (6/765)	2.6% (6/230)	
Self-care			< .001
1 (no problem)	90.1% (689/765)	77.8% (179/230)	
2 (some problems)	8.9% (68/765)	17.8% (41/230)	
3 (extreme problems)	1.0% (8/765)	4.3% (10/230)	
Usual activities			< .001
1 (no problem)	76.6% (586/765)	64.3% (148/230)	
2 (some problems)	20.9% (160/765)	29.6% (68/230)	
3 (extreme problems)	2.5% (19/765)	6.1% (14/230)	
Pain/Discomfort			.552
1 (no problem)	65.6% (502/765)	64.3% (148/230)	
2 (some problems)	32.4% (248/765)	32.6% (75/230)	
3 (extreme problems)	2.0% (15/765)	3.0% (7/230)	
Anxiety/Depression			.612
1 (no problem)	80.5% (616/765)	79.1% (182/230)	
2 (some problems)	18.4% (141/765)	19.6% (45/230)	
3 (extreme problems)	1.0% (8/765)	1.3% (3/230)	
Your own health state today	76.0 ± 16.0	73.8 ± 17.2	.090
(0: bad to 100: excellent)	76.0 ± 16.0	73.8 ± 17.2	.090
Median (IQR)	80.0 (70-90)	75.0 (60-85)	
EQ-5D Index	0.87 ± 0.16	0.83 ± 0.20	.003
Median (IQR)	0.85 (0.81-1)	0.84 (0.78-1)	
Change from Baseline to 30 days	0.01 ± 0.17	-0.01 ± 0.19	.163
Median (IQR)	0.00 (-0.03-0.07)	0.00 (-0.07-0.04)	
Change from Discharge to 30 days	0.06 ± 0.16	0.05 ± 0.19	.392
Median (IQR)	0.01 (-0.6-0.7)	0.01 (-0.9-0.6)	

Data are presented as means ± standard deviation, unless stated otherwise.
P-values ≤ 0.05 were considered statistically significant.
IQR= interquartile range

Discussion

This study demonstrates that octogenarians can safely be treated by EVAR with a 30-day mortality rate of < 2%. Placement of the Endurant stent graft had a technical success rate of more than 99% in both groups, and there was no difference in the number of secondary endovascular procedures or conversion to open surgery between groups. These results compare well with the existing literature on EVAR in octogenarians, including the Eurostar registry.[1,3,11-16] The 30-day mortality rate is at the low end of the spectrum reported previously, possibly reflecting improvements in devices and the perioperative care of octogenarians.

An interesting but previously reported finding is the greater aneurysm diameter and increased neck angulation in octogenarians, suggesting that treatment of the disease occurs at a more advanced stage in elderly patients.3 The infrarenal neck angle of octogenarians was 29 ± 24 degrees versus 34 ± 24 degrees fot the younger cohort, and one may wonder whether such small differences play a fundamental role in daily practice. Octogenarians had higher ASA classifications and a higher prevalence of renal impairment. Advanced stage abdominal aneurysms have been proven less suitable for EVAR, with increased rates of aneurysm-related death, all-cause mortality, and rupture.[17] Despite somewhat more complex aortic anatomy and more comorbidities, octogenarians had early postoperative outcome quite similar to that of the younger patients. Hypothetically, it would appear that, assuming they always have larger aneurysms and more angulated necks, octogenarians are actually less suitable for EVAR, which is supported by the observation that a correction of type I endoleak was more frequently reqiured in octogenarians. However, whereas frequent and accurate monitoring for endoleak development or stent graft migration is essential after EVAR in a younger population, these are of much less importance in the elderly with a natural limited life expectancy. This is further confirmed by the reported results after EVAR of an annual rate of aneurysm-related death of large aneurysms of 1% in the first 3 years which accelerated to 8.0% in the fourth year, which showes that the risk increases only slowly over time.[17] In the present study, anatomical differences did not lead to a lower technical success rate or an increased need for early secondary interventions in octogenarians. Studies with a prolonged follow-up could further elucidate this anatomical debate in the elderly .

In this study a relatively high percentage of general anesthesia was used. Many clinicians prefer local anesthesia, especially in patients at increased surgical risk. Various studies show that general anesthesia for EVAR is associated with increased postoperative length of hospital and ICU stay and more morbidity.[18-20] Speculatively, greater use of local anesthesia might be predicted to reduce morbidity, length of hospitalization, and possibly time to recovery of normal activities. In octogenarians, although not contributing to more major adverse events in this group, both the duration of the procedure and operative blood loss were higher compared with younger patients. The main reason for this observation may relate to the less favorable anatomy of the aneurysms in the older group. But despite the higher frequency of adverse events this did not reach statistical significance, and the rate is considerably less than what has been reported after open surgical repair.[15]

This is one of the few studies that specifically evaluated the quality of life of octogenarians after EVAR. The current data documents significant differences in preoperative quality of life with reduced perceptions of mobility, usual activity and self-care in the octogenarians.

While there was some delay in quality of life recovery in the older patients, specifically with regard to usual activities at 30 days, most elements of health status had recovered to baseline. Interestingly, the younger patients had reductions in the level of their anxiety/ depression at discharge and 30 days, while older patients maintained their baseline levels through 30 days.

The length of recovery to baseline functional level attains particular importance in octogenarians with more limited life expectancy. Prior studies have shown that patient-reported health-related quality of life after EVAR is significantly impaired in the early postoperative period but returns to baseline by 6 months.[21] Another study documented reduced mobility/physical ability among the elderly.[22] Our results are similar to the findings of prior work, but the current data suggest that the recovery may occur early, even within 30 days. The three major randomized controlled trials (EVAR 1 and 2 and the Dutch randomized Endovascular Aneurysm Management [DREAM] trial) comparing EVAR and open repair reported conflicting results on outcome of quality of life.[23-25] For instance, EVAR 1 found a significant difference in favour of EVAR after the first month, which canceled out after longer follow up. The DREAM trial found comparable results after 30 days but a significant difference after 6 months in favour of open repair. This last outcome is not unique and is also more recently been shown.[26] A systemic review in order to compare utility outcomes between EVAR and open repair was unable to reach a clear conclusion due to the low number of studies and inconsistent findings.[27] Several individual institutional studies on the other hand report a similar effect on quality of life after EVAR or open repair.[28,29] These conflicting results make an adequate comparison with open repair difficult.

The current study has some limitations. Even though the registry had limited inclusion/ exclusion criteria and procedural specifications, all patients included were suitable for elective surgical repair of AAA with an endovascular stent graft. It is known from current literature that many AAAs are anatomically unsuitable for endovascular repair.[30,31] This inevitably has lead to a selection bias of anatomically suitable, and therefore preferable, aneurysms. Recently, it has been shown that the reduction in mortality between EVAR and open repair in an acute setting is unlikely to be from a selection bias based on anatomic AAA configuration alone.[32] Whether this relation with anatomical suitability also applies in an elective setting has yet te be determined. Moreover, the current data were derived from an observational, noninterventional study, and therefore it may not be excluded that in certain octogenarians treatment was refused, thereby possibly inducing a selection bias. There also was a difference in gender between octogenarians and the younger cohort. Whether this difference has affected the results may not be concluded from the present data.

In the present study, 1.8 % (5/274) of the octogenarians had an aneurysm diameter smaller than 5.5 cm. Although this does not match with the internationally accepted indications for intervention, we do not believe that this either positively or negatively has affected the outcome. Moreover, this small group of patients also includes those with a rapid aneurysmal growth (>= 0.5cm in the last 6 months). This rapid growth justified the surgical intervention, also in octogenarians. We support the discussion of the adjusted aneurysm diameter in octogenarians if there is an ascertainable growth and adequate follow up is possible. Importantly, the current study has follow-up to 30 days only. The 30-day morbidity and mortality rate, however, is a widely accepted time frame for early postoperative complications. As octogenarians are considered to be frailer when compared to younger patients, an increased complication rate may have been expected, which subsequently could have affected their early quality of life. Early quality of life, in turn, is extremely important fot the elderly, as their life expectancy is short. The ideal time frame of quality of life assessment after EVAR is unknown and clearly, longer-term data of at least 12 months will be necessary to more fully elucidate patient morbidity, quality of life issues, and the interplay between the two.

Conclusion

Octogenarians can safely undergo EVAR with a high rate of technical success, low short-term morbidity and mortality, and good recovery of quality of life indexes by the 30-day postoperative time point. This age group appears ideal for treatment with stent graft repair in those with appropriately sized aneurysms and anatomy suitable for an endovascular solution.

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CHAPER 4

SAFETY AND EFFICACY OF CAROTID ENDARTERECTOMY IN OCTOGENARIANS

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ABSTRACT

Objective

To evaluate the outcome of carotid endarterectomy (CEA) in octogenarians.

Materials and Methods

From January 2005 to July 2010 all CEA patients were prospectively recorded. Patients were categorized into those aged < 80 and ≥ 80 years. Primary outcome measures were hospital length of stay (HLOS), mortality, any stroke and post-procedural complications.

Results

In total 477 patients with carotid artery stenosis were treated by means of CEA. Seventy-one patients (13%) were ≥ 80 years and 477 (87%) patients < 80 years. Median HLOS was 3.0 days (IQR 2-5) for the entire cohort with a median of 3 days (IQR 2-4) for patients < 80 years and 4 days (IQR 2-7) for patients ≥ 80 years (P= .0001). Fifteen patients (3%) had an early adverse neurological event with 7 patients (1.3%) developing a TIA, 2 patients (0.3%) a minor stroke with full neurological recovery and 6 patients (1.1%) had a major stroke. Forty patients (6.8%) had a postoperative nerve injury. No statistical differences were observed between the younger (< 80 years of age) and older (≥ 80 years of age) group despite a significant difference in postoperative delirium (POD) (P< .0001). During follow-up, more fatal cardiac events occurred in the octogenarians group (4.2% vs. 0.4%, P= .02). Kaplan-Meier analysis revealed a significantly better survival for the younger patients (log rank P= .04).

Conclusions

Octogenarians who suffer from carotid artery stenosis can be safely treated by CEA. The increased incidence of POD is an important finding and requires extra attention in this vulnerable group.

Introduction

The safety and efficacy of carotid endarterectomy (CEA) for selected patients with symptomatic carotid stenosis or severe asymptomatic stenosis have been proven in various clinical trials and meta-analyses as a superior treatment compared to medical therapy alone in the prevention of stroke.[1-3] However, in the past advanced age has been associated with an increased risk for complications after CEA.[4,5] In the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial no difference was observed between CEA and carotid artery stenting (CAS) in patients with an increased surgical risk. In this trial, elderly patients were frequently offered replacement therapy by CAS as a less invasive alternative.[6] However, contrasting results are increasingly reported and the indication for CAS or CEA in the elderly patients have become the subject of debate. Both a sub analysis of the SPACE study and a recent meta-analysis of the three major randomized controlled trials between CEA and CAS, age (≥ 70 years) significantly modified the treatment effect in favour of CEA.[7,8] The multicenter Carotid Revascularization Endarterectomy vs. Stent Trial (CREST) reported in their interim results that the periprocedural risk of stroke and death after CAS also increases with age with a 30-day stroke or death rate of 12.7% for octogenarians.[9] This even led to the withdrawal of asymptomatic octogenarians (≥ 80 years) from the trial. Conflicting with the abovementioned results are several individual institutional studies reporting good results in high risk and elderly patients after both CEA and CAS.[10-13] Although most studies are reporting results of octogenarians as high risk group, there is increasing evidence that increased risk already starts at the age of 70.[7,14] In all it seems clear that there is a significant interaction between age and the treatment risk of stroke and/or death after carotid artery revascularisation. At the same time, the population in most Western countries is ageing rapidly, and therefore an increasing number of octogenarians will present at the outpatient clinic for treatment. Given the current controversies it is both interesting and important to compare the outcome of these elderly patients. The threshold age of 80 years seems a good cut-off point for analysis because, although arbitrary, current literature has used this cut-off in binary analyses[9-14]. The current study was undertaken to evaluate whether age alone should be a reason to refrain from treating elderly patients with a carotid stenosis by means of CEA.

Materials and Methods

From January 2005 to July 2010 all patients in two participating hospitals (one academic centre and one large community hospital) undergoing carotid artery revascularisation by means of CEA were prospectively recorded in a vascular registry. In principle, CEA was the preferred treatment. If there was a high risk for open surgery, a risk assessment was done based on several criteria including severe cardio-pulmonary disease, 'hostile neck' due to prior surgery or radiation therapy, a very distal carotid bifurcation, inflammatory diseases (Takayasu) or pre-existent laryngeal nerve paralyses. Patients who met these criteria were considered for CAS. The CAS data were, due to the low number (n=32) and as a consequence a possible bias, not included in the analysis.

Included in the database were age, sex, degree of stenosis, atherosclerotic risk factors (diabetes mellitus, smoking, hypertension, statin use and dyslipidaemia), cardiac status and pulmonary disease (SVS (Society of Vascular Surgery) classification), renal function, pre-operative haemoglobin levels, hospital length of stay (HLOS), post-procedural cranial nerve damage, post-procedural neurological status, post-operative complications, neurological status during follow-up, and mortality. Long-term survival and mortality were determined by reviewing the computerized hospital registry and charts and by contacting the patients' general practitioner. The baseline and clinical patient characteristics are shown in Table 1.

General considerations and indications for surgery have been previously published by our group.[15] In short; all CEA's were performed under general anaesthesia, with antibiotic prophylaxis (1000mg Cephazolin) and by a single group of board certified vascular surgeons. Patients were monitored intraoperative with continuous electroencephalographic (EEG) monitoring. All patients were prescribed aspirin 100 mg/day preprocedurally and received 5000 IU heparin intravenously before arterial clamping. At the academic centre also intraoperative transcranial Doppler monitoring was performed. Intraoperative shunting was used selectively in those patients who showed changes in EEG after carotid clamping. The arteriotomy was preferably closed with an autologous vein or, in the absence of a suitable vein, with a synthetic patch. In selected cases (internal carotid artery ≥ 5mm in diameter) the arteriotomy was closed primarily with a running suture. All patients had duplex ultrasound scanning 6 weeks postoperatively to determine the degree of residual stenosis. Both centers were aimed at treating patients within 2 weeks after their index event.

Patients were categorized into those aged < 80 and ≥ 80 years. Post procedural (major or minor) strokes, surgical and medical complications, HLOS, and death were prospectively recorded. Endpoints for this study were defined as death or recent follow-up within 6 months of data analysis to ensure that the patient was still alive. Primary outcome measures were mortality, any stroke (major or minor), post-procedural complications between the two age groups and HLOS. Survival curves were developed for the two cohorts (age < 80 or ≥ 80 years).

Statistical analysis

Differences between categorical variables were tested with Pearson's χ^2 test (2 variables) or Kruskal-Wallis test (> 2 variables). Survival rates were calculated by means of Kaplan-Meier analysis. Differences in survival were determined using log-rank testing. Differences between means were tested with Student's two-tailed test (normally distributed continuous variables) or Mann-Whitney U test (skewed continuous variables). Skewed continuous variables are shown as median (interquartile range). One sample Kolmogorov–Smirnov test was used to test distribution of data. Two-tailed P-values were used throughout and significance was set at $P < 0.05$. Data are presented as means ± standard deviation, unless stated otherwise. All statistical analyses were done with the Statistical Package for the Social Sciences (SPSS 16.0.1, SPSS, Chicago, IL, USA, 2007).

Table 1. Baseline and clinical patient characteristics.

Parameter	Number of mean ± SD a (percentage of range)			
	Predictor available (%)	Age < 80 years	Age ≥ 80 years	P value
Number	548 (100%)	477 (87%)	71 (13%)	NA
Age	69±10 (25-91)	67 ± 9 (26-83)	82 ± 3 (80-91)	NA
Male gender	395 (72%)	345 (72%)	50 (70%)	.739
Smoking[a]	216 (39%)	198 (41%)	18 (25%)	.005
Hypertension	447 (81%)	365 (76%)	50 (70%)	.250
Cardiac status[b]	228 (42%)	192 (40%)	36(51%)	.020
Pulmonary disease[c]	61 (11%)	55 (11%)	6 (8%)	.636
Diabetes mellitus	111 (20%)	104 (22%)	7 (10%)	.009
Dyslipidaemia	356 (65%)	319 (67%)	37 (52%)	.009
Anticoagulant therapy	529 (96%)	462 (97%)	67 (94%)	.235
Use of statins	510 (93%)	442 (93%)	68 (96%)	.760
Pre-operative haemoglobin (mmol/l) median (IQR)	8.8 (8.0-9.3)	8.9 (8.1-9.3)	8.2 (7.8-9.0)	.139
Impaired renal function[d]	116 (21%)	97 (20%)	19 (27%)	.265
Index symptoms				
Asymptomatic	58 (10%)	57 (12%)	1 (1%)	.003
Amourosis fugax	84 (15%)	75 (16%)	9 (13%)	.529
TIA	210 (38%)	182 (38%)	28 (39%)	.790
CVA	232 (42%)	195 (41%)	37 (52%)	.109
Degree of stenosis (%)				
0-50	1 (0.2%)	1 (0.2%)	0	.699
50-70	56 (10%)	47 (10%)	9 (13%)	.464
70-99	491 (90%)	429 (90%)	62 (87%)	.464
Shunting (%)	42 (8%)	35 (7%)	7 (10%)	.667
CEA with patching	400 (73%)	362 (76%)	38 (53%)	.001

Results presented as number or mean ± SD (standard deviation) or stated otherwise.
P-values ≤ 0.05 were considered statistically significant
NA, not applicable
[a] *Relates to current smoking status, including abstinence < 1 year*
[b,c] *SVS (Society of Vascular Surgery) stage ≥ 1*
[d] *Defined as creatin level ≥ 2.4mg/dl*
IQR = interquartile range
TIA = transient ischemic attack
CVA = Cerebrovascular accident

Results

Study cohort

In total 548 patients with carotid artery stenosis were treated by means of CEA. Seventy-one patients (13%) were ≥ 80 years and 477 patients (87%) were < 80 years. The operation side was equally divided with left and right side respectively 50.8% and 49.2%. The mean age of the total cohort was 69±10 years (25-91) with a mean age of 67 ± 9 (26-83) years in the younger cohort and 82 ± 3 (80-91) in the octogenarians group. There was an unequal distribution in sex with 395 men (72.4%) and 153 women (27.6%). Baseline characteristics are listed in Table 1. Younger patients were more likely to smoke (P= .005), suffer from diabetes (P=.009) or dyslipidaemia (P= .009). 39 % of patients were currently smoking or had ceased smoking in the last year. The majority of patients (90.3%) had symptomatic disease prior to surgery with 14.1% suffering from amaurosis fugax, 35.8% have had one or more transient ischemic attacks (TIA) and 39.2 % a minor ischaemic stroke. Octogenarians suffered more often from an ischemic stroke prior to surgery compared to the younger cohort (resp. 48% vs. 38%). More than 98% of octogenarians had symptomatic disease. Twenty-one percent of patients < 80 years had a contralateral stenosis of ≥ 80% versus 18% in the octogenarians' cohort. Ninety-six percent of patients used an anti-platelet agent prior to surgery.

In 283 CEA procedures (51.6%) an autologous vein was used for arteriotomy closure, in 117 patients (21.4%) a synthetic patch and 148 (27%) were closed primarily. Mean arterial clamping time was 30 minutes (range 16-63, clamping time prior to shunt placement not included).

Table 2. Comparison of perioperative and 30-day outcome after CEA between patients < 80 and ≥ 80 years.

Event	Age < 80 years	Age ≥ 80 years	P value
Postoperative neurological deficits, n (%)	14 (2.9)	1 (1.4)	.699
Transient ischemic attack	7 (1.5)	0	NA
Minor stroke	2 (0.4)	0	NA
Major stroke	5 (1)	1 (1.4)	NA
Myocardial infarction, n (%)	2 (0.4)	0	.916
Nerve injury*, n (%)	37	3	.523
Haematoma / rebleeding, n (%)	27 (5.6)	7 (9.3)	.080
Delirium, n (%)	8 (2)	8 (11)	.0001
Hospital length of stay, median (IQR)	3 (2-4)	4 (2-7)	< .0001

NA, not applicable
** Including cranial and peripheral nerve injuries as well as (reversible) neuropraxia*
IQR= interquartile range

30-day outcome

Median HLOS was 3.0 days (IQR 2-5) for the entire cohort with a median of 3 days (IQR 2-4) for patients < 80 years and 4 days (IQR 2-7) for patients ≥ 80 years (P=.0001). In 8% of cases a shunt was required perioperatively. A total of 15 patients (3%) had an early adverse neurological event with 7 patients (1.3%) developing a TIA, 2 patients (0.3%) a minor stroke with full neurological recovery and 6 patients (1.1%) had a major stroke. Forty patients (6.8%) had a postoperative nerve injury (including peripheral nerve injuries as well as neuropraxia. 0.5% of nerve injuries were irreversible. Postoperative neck hematoma and/or rebleeding after CEA were observed in 34 patients (6%) in which 12 patients needed an intervention. No statistical differences were observed in the above mentioned complications between the younger (< 80 years of age) and older (≥ 80 years of age) group (Table 2). A total of 16 patients (2.9%) developed postoperative delirium with 8 patients (1.4%) younger than 80 years and 8 patients (10.6%) older than 80 years of age (P< .0001).

Other 30-day complications

A total number of 89 complications were recorded. Multiple complications could occur in one patient. Four patients developed pneumonia during follow-up necessitating additional treatment. Eight patients had a urinary tract infection and 4 patients developed a wound infection. The remaining complications were classified as miscellaneous with postoperative hypertension most often observed. There were no differences in the above mentioned complications between the two cohorts except for a higher incidence of pneumonia in the octogenarians group (4.2% vs. 0.2, P= .0001).

Late outcome

Follow-up duplex ultrasound scanning 6 weeks postoperatively was performed in 91% of the patients. In the octogenarians only 2% had a residual stenosis of ≥ 40%. In the younger cohort 7% had a residual stenosis of ≥ 40%. In 1% of patients an additional CAS procedure was performed and in 1% a redo CEA due to thrombosis. In the octogenarian's cohort a wait and see policy was performed and no further intervention was necessary during follow-up. The mean follow-up for the entire cohort was 25 months (range 0.3-75 months). During follow-up 44 (9%) out of 477 patients younger than 80 years of age died, compared to 12 (17%) out of 71 patients older than 80 years (P=.004). Seven patients (1.3%) had died from a major neurological event. Other causes of death included a cardiac event in five patients (1%), a pulmonary cause in 6 patients (1.1%), multi-organ failure in 6 patients (1.1%) and as a consequence of a malignancy in another 13 patients (2.4%). There were more fatal cardiac events in the octogenarians group (7.1% vs. 0.6%, P=.002) during follow-up. Two-year actuarial survival after CEA was 93% for patients younger than 80 and 92% for those older than 80. At five years follow-up, these figures were 81% and 67%, respectively. No statistical difference was observed between the younger (< 80 years of age) and older (≥ 80 years of age) group regarding neurological events (TIA, minor or major ischemic stroke) (Table 3). Kaplan-Meier analysis for the probability of patient survival following treatment of carotid stenosis by CEA revealed a significantly better survival for the younger patients (log rank test P= .04) (Figure 1).

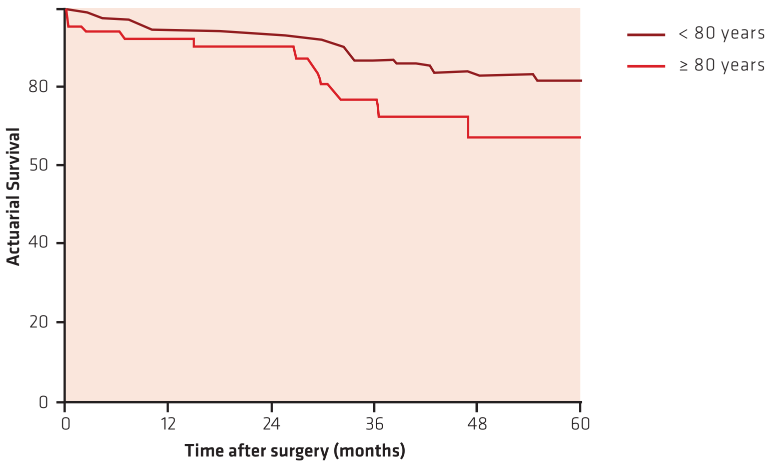
Table 3. Comparison of long-term neurological outcome after CEA between patients < 80 and ≥ 80 years.

Event	Age < 80 years	Age ≥ 80 years	P value
Ipsilateral TIA, n (%)	10 (2)	1 (1.4)	.723
Ipsilateral minor stroke, n (%)	7 (1.4)	0	.687
Ipsilateral major stroke, n (%)	10 (2)	1 (1.4)	.723
Death due to ipsilateral stroke, n (%)	3 (0.6)	0	.897
Contralateral TIA, n (%)	3 (0.6)	0	.897
Contralateral minor stroke, n (%)	1 (0.2)	0	.954
Death due to contralateral stroke, n (%)	0	1 (1.4)	.634
Cardiovascular death	3(0.6)	5 (7.1)	<.0001

TIA, transient ischemic attack

Figure 1.

Probability of patient survival according to the Kaplan-Meier method following treatment of symptomatic carotid stenosis by CEA; comparison of patients < 80 years of age and ≥ 80 years. There is a significantly better survival for the younger patients (log rank P=.04). Standard error does not exceed 10% during follow-up but will most likely do in the octogenarians group after > 4 years



No. at risk	0	12	24	36	48	60
< 80 years	467	349	220	143	94	32
Standard error	0%	1.1%	1.3%	2.2%	2.6%	5.0%
≥ 80 years	70	51	32	19	12	6
Standard error	0%	3.3%	4.7%	7.8%	9.0%	9.0%

Discussion

This study shows that octogenarians who suffer from carotid artery stenosis can be safely treated by CEA. More specifically, there was no statistical difference in number of early or late ipsi- or contralateral neurological events between the younger (< 80 years of age) and older (≥ 80 years of age) patients. Due to a higher number of fatal cardiac events in the elderly, there was a statistical difference in overall mortality in favour of the younger cohort. This difference seems more in line with the natural life expectancy of the elderly patients and overall frailty than it is related to the procedure. Our results correspond well with the results reported in the literature and further confirm the safety of CEA in octogenarians.[10,11,14,16] Although so far the indications for CEA in octogenarians are somewhat uncertain, the current study and various other publications establish clear criteria and risk factors so that octogenarians can be handled safely and with excellent results.

With the emergence and further development of CAS, increasing attention is given to the high risk of CEA. CAS has been proposed as a saver alternative to CEA in these high risk patients. The SAPPHIRE-trial, comparing CEA to CAS, only enrolled patients who were considered "high risk" for CEA. They found similar results regarding perioperative risk for stroke (CAS, 3.1%, CEA 3.3%, P= .94) and mortality (CAS, 0.6%, CEA 2.0%, P= .29). Although not included in this analysis (due to the low numbers treated) we found a significantly higher mortality in our hospital after CAS during follow-up (N=32, data not shown) but no difference regarding the occurrence of post-procedural neurological events (TIA, minor or major ischemic ipsilateral stroke) between the two age groups. This difference was mainly determined due to more fatal cardiac events in the octogenarians' cohort. The difference in mortality however cancelled out after a sub analysis among octogenarians. Although a proper conclusion cannot be drawn on these results and with the obvious selection bias, the outcome seems more related to the comorbidities that initially have led to CAS, rather than the procedure itself.

Our study focuses both on the safety as well as efficacy of CEA. We found a two- and five-year actuarial survival after CEA for octogenarians of 93% and 67%, respectively. With a mean survival for octogenarians in the Dutch population (matched for both age and sex) of 6.1 years (median 3.9 years) it appears that octogenarians still live long enough to achieve a decrease in stroke morbidity and therefore still benefit from an operative intervention.[17] When a cerebrovascular event occurs, it leads to important functional and independence loss and sometimes permanent functional impairment.[18,19] Preventing such a devastating event is of great importance in an already vulnerable group such as octogenarians.

We found a significantly higher incidence of post-operative delirium (POD) among octogenarians after CEA. When delirium was present or suspected a geriatrician was consulted and the diagnosis was confirmed based on the DSM-IV-TR criteria.[20] We would have strongly preferred that all patients had undergone a proper DOS assessment. Unfortunately, due to the retrospective nature of this study this was not possible. This may have led to an underestimation of delirium incidence by missing clinical subtypes such as hypoactive delirium or the unclassified type which account for respectively 29% and 7% of delirium subtypes.[21] Atherosclerosis of the carotid arteries is a known risk factor for the development of delirium after coronary artery bypass surgery.[22] The increased risk of POD after this type of surgery may possibly be caused by direct manipulation of the aortic arch which may lead to disrupted plaques and thrombi-emboli. This mechanism may also apply to carotid surgery.[23] POD is associated with short-term effects such as prolonged hospitalization and could very well have contributed to the significantly prolonged HLOS for octogenarians in our series. Octogenarians should be considered a high risk population for POD and by starting preventive treatment or aggressive assessment during hospitalization perhaps the incidence of POD and ultimately HLOS could be reduced.[24]

There are several drawbacks in this study that need to be addressed. This concerns a retrospective cohort study and no randomisation was performed which probably has led to some form of selection bias. Also, we report the results of two individual centres. Therefore, our results are determined by different surgical techniques. The main difference is the higher rate of primary closure of the carotid artery in one clinic. Strict requirements for this technique was an internal carotid artery diameter of ≥ 5mm. Nevertheless, there were no significant differences in outcome or complications between the participating hospitals. Even though the literature shows that patch angioplasty reduces the risk of subsequent stroke and restenosis, recent studies show that in conjunction with contemporary medical treatment, primary closure may yield results comparable to patch angioplasty.[25,26] Although the 5-year restenosis rate after primary closure is higher compared to patch angioplasty, both complication rates (bleeding, infection, pseudo aneurysm formation) and combined 30-day stroke and death rates are at least as good if not better.[26]

Twenty percent of our patients had an asymptomatic stenosis. Although this is just a small percentage of the studied population, most studies deal only with symptomatic disease. However, recently it has been shown that these patients certainly benefit from an intervention where a significant risk reduction from a disabling or fatal stroke can be achieved.[27] Secondly, > 98% of octogenarians in our study had symptomatic disease and this group had our specific focus.

Conclusion

This study demonstrates that octogenarians can be safely treated by carotid endarterectomy with perioperative stroke risks comparable with those of younger patients. Octogenarians with symptomatic carotid stenosis should be offered CEA as initial treatment and age alone is no reason to refrain from treating elderly patients with a carotid stenosis. CAS can be justified for patients whose medical comorbidities or cervical anatomy make them questionable candidates for CEA.

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SECTION II

POSTOPERATIVE DELIRIUM IN VASCULAR SURGERY PATIENTS.

CHAPER 5

THE RELATION BETWEEN ATHEROSCLEROSIS AND THE OCCURRENCE OF POST-OPERATIVE DELIRIUM IN VASCULAR SURGERY PATIENTS

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ABSTRACT

Old and frail patients undergoing vascular surgery seem at great risk of developing post-operative delirium (POD). The aim of this review was to identify risk factors for the development of POD in vascular surgery patients. Different aetiological factors have been identified, such as high age, excessive blood transfusion, pre-operative cognitive impairment and depression. Mounting evidence supports a role for inflammation and tobacco exposure in the development of POD. Vascular surgery patients differ from the general surgery population because they suffer from both loco-regional and systemic atherosclerosis. Although current scientific evidence can not fully link both entities, evidence is growing that suggests a relationship between systemic and cerebrovascular atherosclerosis and the development of POD.

Introduction

Cardiovascular disease is a common problem in the general population, affecting an essential part of adults over the age of 60 years. The lifetime risk for individuals at the age of 40 is 49% in men and 32% in women, making it a substantial healthcare burden.[1] The main process in the development of cardiovascular disease is atherosclerosis which already starts during adolescence and may cause plaque formation and thrombo-embolic events later in life. Among the multiple risk factors established for cardiovascular disease, high age remains one of the strongest predictors for a cardiovascular event.[2,3] Furthermore; there is a strong relationship between the number of vascular beds affected and the risk for additional atherosclerotic events. For example, patients with a low ankle-brachial index (< 0.9) also have a significantly increased risk for fatal myocardial infarction, emphasising that atherosclerosis is, and acts like, a systemic disease.[4]

For elderly patients admitted to the hospital postoperative delirium (POD) is a common and important complication. It is defined as an acute disorder of attention and cognition and is characterized by fluctuating symptoms of inattention, disturbance of consciousness and disorganized thinking.[5] Not only is it the most common complication in elderly (> 65 years) patients, affecting about 11-60% during hospital admission, POD is also associated with short-term effects such as prolonged hospitalization and institutionalization (due to functional loss, loss of independence and the inability to return to ones home) and increased medical costs, but also long-term effects such as persistent functional decline and death.[5-12]

With the population ageing at an unprecedented rate, more elderly patients are being considered for surgery, which inevitably will result in an increased incidence of POD in the near future. In current literature, various risk factors for the development of POD in the elderly have been identified. General risk factors are mainly age-related and include high age, pre-existing comorbidities, pre-existing dementia or cognitive impairment, and a history of prior delirium.[10-12] The overall incidence of POD estimated at 11-24%, with an incidence up to 60 % in high risk geriatric patients. There is a wide-spread variation in incidence between different types of surgery with few outliers carrying an increased risk, including cardiac-, orthopaedic- and vascular surgery. In a recent systematic review, addressing preoperative risk assessment for POD after non-cardiac surgery (gastrointestinal surgery not included), the highest incidences were found in abdominal aortic surgery (46-52%).[5] POD and atherosclerosis often occur together in elderly patients, but it is questionable whether high age alone is the common denominator. We therefore hypothesized that atherosclerosis, as a systemic disease, is the main reason for the increased incidence of POD in vascular surgery patients when compared to the general surgery population. The purpose of this study was to identify prognostic factors for the occurrence of POD within the field of vascular surgery and to find out whether atherosclerosis causes an increased risk.

Incidence and risk factors of post-operative delirium in vascular surgery

Vascular surgery patients are among patients at highest risk for developing POD. At first this seems to be caused by the fact that vascular patients are both old and frail and usually present with multiple comorbidities, including cerebrovascular disease. Yet notwithstanding these known risk factors, an evident pathogenesis of POD is still unclear.[13] Inouye et al. was able to identify four baseline risk factors for the development of POD in a general population which included impaired vision, severe illness, cognitive impairment and a high blood urea nitrogen/creatinin ratio. However, a prospective study specifically focusing on risk factors and outcome in POD among elderly patients was unable to identify an underlying cause in 88% of subjects who developed POD.[11,14] These results further underline the heterogeneity of POD and its challenges in treating it solely based on these biological factors. With regard to the surgical population there are a number of perioperative factors that influence the incidence of POD. Both the amount of intra-operative blood loss and intravenous fluid infusion and a poor pre-operative nutritional status and low body mass index (BMI) are associated with a significantly higher incidence of POD and a longer hospital stay.[15-18] Second, one of the most potent risk factors which may be prevented is pain, which seems to be directly associated with both POD and functional decline.[19,20] No difference exists between intravenous or epidural analgesic modalities on POD, but postoperative opioid administration is associated with an increased risk of POD in elderly patients.[21,22] Furthermore, in an emergency setting the incidence of POD significantly increases, suggesting an even greater awareness of possible POD is needed under these conditions.[5,23]

Few studies focus selectively on risk factors and POD prevention among vascular surgery patients.[15,24-30] (Table 1) A recent review on POD after elective vascular surgery was able to identify various aetiological factors, including age, pre-operative cognitive impairment, depression, and excess interoperative blood transfusion.[28] Unfortunately, due to small sample sizes, heterogeneity and differences in confounding variables, a proper meta-analysis could not be performed. Nevertheless, the influence of inflammation and tobacco exposure emerge from the current data that appear to be particularly applicable to patients who undergo vascular surgery procedures, both of which we will therefore further discuss in detail.

Table 1. Studies on incidence of POD in elective vascular surgery

Study author *	Year	Sample size	Surgery type	Type of procedure(s)	Overall incidence of POD (%)
Böhner et al.[24]	2000	54	elective	AAA, TAA, aortoiliac and peripheral	39%
Sasajima et al.[25]	2000	110	elective	Aortic and peripheral bypass	29%
Schneider et al.[26]	2002	47	elective	Aortic, carotid and peripheral	36%
Böhner et al.[15]	2003	153	elective	Aortic, carotid and peripheral	39%
Minden et al.[27]	2005	35	elective	AAA	23%
Benoit et al.[51]	2005	102	elective	AAA	33%
Koebrugge et al.[30]	2010	107	elective/ emergent	aortoiliac	23%
Bryson et al.[29]	2011	88	elective	Aortic	36%

** Number corresponding with the reference list*
AAA= abdominal aortic aneurysm
TAA= thoracic aortic aneurysm

Inflammation

In a comparative study in patients with asymptomatic peripheral arterial occlusive disease (PAOD), an elevated C-reactive protein (CRP) blood level turned out to be a significant negative predictor in multiple cognitive tests and an impaired visuoconstructive performance, which suggests the presence of a relationship between POD and inflammatory processes.[31] The only study to date that focuses on POD and critical limb ischemia found a highly significant relationship between critical limb ischemia and POD (OR = 3.8; 95% CI = 1.3-10.9).[25] Unfortunately, the expected processes in critical ischemia, such as necrosis with concomitant elevated inflammatory markers, were not further analysed with regard to the risk of POD and thus the relationship is merely suggestive. In view of a potential intervention strategy for POD, Böhner et al. determined a prediction model based on both somatic and psychiatric risk factors in vascular surgery patients and also found a pre-operative elevated (> 3 mg/L) CRP level to be associated with an increased probability for the development of POD.[15] Furthermore, vascular surgery patients who developed POD scored higher pre-operative depression scores, had decreased psychosocial functioning and more cognitive impairment, suggesting the presence of some predisposing factors within this group. Although various studies have found high levels of CRP to independently predict the incidence of delirium, the apparent cause was not clear.[32,33] Even more indicative of a causal relation between POD and inflammation is the substantial evidence that more refined inflammatory markers as cytokines play a vital role.[34] Whereas CRP is an acute-phase protein, and a non-specific marker for inflammation, cytokines are fare more sensitive being specific mediators of the immune system. Current data suggest a pathway of inflammation that culminates in higher concentrations of various markers in peripheral blood.[35,36] Various studies focussing on inflammatory markers as predictor for delirium showed that patients who developed a delirium had significantly elevated levels of interleukins 6 and 8.[37-39] A recent review, investigating the role of inflammation in the pathogenesis of delirium, further confirmed the role of these inflammatory processes in the development of delirium.[34] Despite the selective regulation of the blood-brain barrier, the brain is in fact directly influenced by peripheral cytokines through activation of vascular endothelial cells and perivascular cells in the brain. By propagating the inflammatory cascade, this may then lead to neuron injury.[34] This neuroinflammatory response causes neurocognitive behavioural abnormalities.[40] One of the studies focusing on CRP and activation of vascular endothelial cells also found a close correlation between the two systems, further supporting the concept that inflammatory processes indeed interact with vascular cells.[41] There is increasing evidence that ageing is associated with increased neuroinflammation, manifested as increased levels of activated microglia, the immune cells of the brain.[42] This increased baseline inflammation in the elderly has a priming effect resulting in an enhanced response to peripheral stimuli.[43] This priming of the ageing brain can be a plausible explanation for the increased response to stimuli associated with surgery.

In view of the proposed inflammatory responses, current insights even suggest that atherosclerosis constitutes an autoimmune disease and shares similarities with chronic autoimmune diseases as SLE, rheumatoid arthritis and vasculitis. So it seems that both auto-antigens and peripheral lymphocytes play an important role in the development and regulation of atherosclerotic lesions.[44]

Tobacco

Nicotine consumption is a well known risk factor within the multifactorial pathogenesis of delirium. Particularly within an intensive care population, smoking significantly increases the risk for delirium.[45-47] Patients suffering from vascular disease are known for their nicotine abuse and thus seem to be at increased risk of POD because of this. The causal relation between nicotine abuse and POD is not fully understood but seems twofold. First, cigarette smoking effects are believed to induce neuro-adaptive changes in the brain, especially after cessation. Although these changes are complex, they are related to an increase in neurotransmitter function which shares a common pathway with delirium.[46] Second, atherosclerosis and micro-vascular changes in the brain caused by smoking can lead to impaired cognitive functioning and reserve.[47] Although a different entity, there is a significant relationship between the increased risk on the development of Alzheimer's disease, vascular dementia, cognitive decline and smoking.[48-50]

Clinical proof for these theories is based on several studies: Patients who undergo elective abdominal aortic aneurysm repair are already susceptible for the development of POD. Additionally, there appears to be a strong association between tobacco exposure and POD

(P= .001) in this specific group of vascular surgery patients.[51] Patients developing POD were taking significantly more psychoactive medication, had lower mental status scores and had a significant higher number of smoking pack-years. With age being equally distributed between the studied groups, age ≥ 80 years was also a risk factor for POD. In a second study, focussing on vascular risk factors for POD, the indication for vascular surgery and tobacco exposure again proved to be independent risk factors for POD.[52] After adjustment for age, the associated risk factors for tobacco exposure and vascular surgery were RR 1.6, 95% CI 1.0-2.6 and RR 2.7, 95% CI 1.7-4.2 respectively. Patients with both vascular risk factors and impaired cognitive performance were at double the risk for POD development (RR = 3.2; 95% CI = 2.1-4.9), an effect the authors refer to as "a double gradient effect". Nevertheless the above mentioned results point more towards life-time tobacco exposure than to the current smoking behaviour, suggesting the presence of smoking induced (micro-) vascular changes rather than a direct toxic effect. Further support for this theory comes from a study focusing on smoking and dementia. Compared with never smokers, current smokers had an increased risk of Alzheimer's disease (RR = 2.72; 95% CI = 1.63-5.42) and vascular dementia (RR = 1.98; 95% CI = 1.53-3.12) after adjusting for age, sex, education, blood pressure, and alcohol intake.[53] In non-demented elderly smoking may also accelerate cognitive decline.[54] Whether this is related to POD and causes an increased risk remains unclear.

Atherosclerosis and cognitive dysfunction

Cerebral atherosclerosis and cognitive dysfunction

Atherosclerosis is a systemic disease. Consequently, patients presenting with PAOD are at higher risk for cerebrovascular disease.[55,56] Atherosclerosis in the carotid arteries may lead to both decreased cerebral perfusion and/or micro emboli, suggesting that a decreased cognitive function might be causal to this disease and therefore itself a potential risk factor for POD. One of the studies supporting this hypothesis compared the cognitive performance of PAOD patients with healthy individuals and stroke patients. PAOD patients had a diminished performance of cognitive function and seemed, independent of age, at risk for a continuum of cognitive impairment.[55] A large prospective population-based study (The Leiden 85-plus study), used to asses the relationship of generalized atherosclerosis and cognitive decline, annually scored a large community-dwelling elderly population with a predetermined atherosclerotic burden on various cognitive domains. This study showed that in old age generalized atherosclerosis is indeed associated with cognitive decline.[57,58] In contrast to the expectations, there was no association between generalized atherosclerosis and depressive symptoms, a finding that conflicts with the vascular depression hypothesis.[59,60] This hypothesis proposes that vascular disease underlies mood disorders in some older adults and that vascular disease is associated with a greater risk of cognitive decline and dementia. Rudolph et al. found that mild cognitive impairment and predisposed vascular risk factors, such as hypertension, diabetes, congestive heart failure, previous myocardial infarction and the need for vascular surgery, all independently contribute to the occurrence of POD.[52] Unfortunately all other research conducted in the area of atherosclerosis and POD was done after coronary artery bypass surgery and most papers in this field focussed on aortic atheroma burden and the risk of aortic clamping leading to iatrogenic tromboemboli, which makes comparison with general (peripheral) vascular surgery difficult.[60-67] It seems likely that these patients have a similar high burden and distribution of atherosclerosis. Although both carotid artery and intracranial stenosis have been associated with worse cognitive outcome[62], the literature is contradictory on this point. Whereas Rudolph et al. found a significant association between a higher atherosclerosis score and the incidence of POD, Bar-Yosef et al. found no relationship between aortic atherosclerosis and postoperative cognitive dysfunction.[61,64] The former uses a 0-3 scale, points given for carotid stenosis > 50%, three or more affected cardiac vessels and moderate or severe ascending aortic plaques, the latter focuses solely on the proximal aorta atheroma burden which therefore seems less relevant to the general vascular surgery population.

Thrombo-embolic events

Although the relationship between atheroma burden (%) of the proximal aorta and the development of POD has been clearly demonstrated, interestingly the current results contribute to the lack of a clear consensus on its true pathophysiology.[63] Although the relationship between the degree of cerebral micro emboli and aortic atheroma is evident, its influence on cognition remains unclear.[65] Whether the development of POD is related to thromboembolic events, due to aortic atherosclerosis, remains therefore also unanswered. A recent study, designed to determine the association between cerebral micro emboli and POD in cardiac surgery patients, found no significant difference after short-term follow-up between the number micro emboli count and the occurrence of POD.[66] They concluded that the long-term clinical impact of cerebral micro emboli remains unknown. The increased risk of POD after coronary artery bypass graft surgery may possibly be caused by direct manipulation of the aortic arch which may lead to disrupted plaques and thrombi-emboli. Whether the current results also apply to general vascular surgery patients is therefore difficult to estimate. Although hypothetically the perioperative stress in general vascular surgery patients could lead to similar plaque disintegration, instability and thrombi, this can not be reliably determined.

Discussion

The development of POD in vascular surgery patients seems not just a process of combined comorbidities and high age but more so the inability to adjust to changes in stress, physiology and environment. We have explored the incidence and the multifactorial pathogenesis of POD in vascular surgery patients and attempted to demonstrate a relationship between atherosclerosis and POD. The known literature on delirium and POD is overwhelming and confirms the complex composition which leads to POD. In the vascular surgery population there are several general factors, such as blood loss, analgesics use, emergency surgery and nutritional status that could potentially be affected by preventive measures by incorporating them into risk-reduction strategies of postoperative POD. Our study has identificatied groups of patients that are at increased risk for POD development. First, there appears to be an association between the emergence of POD and smoking. Although current literature falls short in giving a clear statement, the relationship with the number of pack-years smoked clearly suggests (micro) vascular damage as causal factor, although neuroadaptive changes may also play a role. With the combination of vascular surgery and tobacco exposure, as independent risk factors for POD, it is highly suggestive that an increased atherosclerosis burden is the causal factor. Whereas smoking cessation was formerly advised in favour of wound healing, patients with vascular disease should also cease smoking in time to reduce the chance of POD at time of surgery.

Another interesting observation is an apparent relationship between inflammatory processes and the risk on POD. The origin of these elevated inflammation markers seems twofold. The first, and most obvious reason, is ischemia-related necrosis due to PAOD which is frequently seen in vascular patients, especially in advanced disease. Second, there is increasing evidence that atherosclerosis acts as an autoimmune disease, in which both auto-antigens as well as peripheral lymphocytes play an important role in the development and regulation of atherosclerotic lesions. As elderly patients already have increased neuroinflammation, this can lead to an amplified inflammatory response to peripheral and central stimuli. However, it is very likely that both mechanisms co-exist and both can be a potential target for intervention.

Vascular surgery patients should be considered a highly vulnerable population and are more susceptible for postoperative complications, such as POD, than their counterparts in general surgery. This increased vulnerability is frequently referred to as frail, which is defined as the risk for adverse outcomes due to losses in different domains of functioning, related directly to these adverse processes.[68] Robinson et al. already suggested that it is more a matter of physiological vulnerability and that baseline frailty characteristics play a vital role in the development of POD.[11] At our centre, the Groningen Frailty Indicator (GFI) has been developed to pre-emptively identify patients at risk for POD and other adverse outcomes. Although primarily designed for oncogeriatric patients it is already validated among different patient groups in various publications.[69-72] A recent review on delirium prevention and management stresses the importance of secondary prevention of POD, including early detection and treatment.[73] Unfortunately very few studies focus on risk factors and POD prevention among vascular surgery patients and an accurate pre-screening tool is currently lacking. Although specialized geriatric wards and multicomponent interventions have been proven to prevent POD and improve outcome, in many hospitals this is probably not feasible.[14,74] Recently a prospective study was conducted at our hospital that demonstrated that the GFI is a significant predictor for the occurrence of POD.[75] The GFI can be helpful in the early identification of a select group of high risk patients with respect to the development of POD after vascular surgery. By identifying these patients during the preoperative outpatient evaluation, appropriate preventive arrangements, such as preoperative geriatric consultation, can be implemented. This seems particularly important because proactive geriatric consultation has been proven to reduce both delirium incidence and severity after surgery.[76,77] To date, there is no consensus regarding the efficacy of pharmacological treatment for delirium prevention. Although prophylactic low dose haloperidol may reduce severity and duration of delirium episodes, there is no effect on the POD incidence. When POD still occurs, the pharmacological treatment is primarily based on antipsychotics.[78] In particular low dose haloperidol may be effective in decreasing the degree and duration of delirium in post-operative patients.[79]

POD is associated with various long-term effects such as persistent functional decline, and death. Although it is generally assumed that atherosclerosis is a risk factor for depressive symptoms, 'the vascular depression hypothesis', this could not be demonstrated in the Leiden 85-plus study. POD on the other hand is statistically significantly associated with long-term psychosocial distress with symptoms of depression and/or anxiety.[80] Interestingly preoperative anxiety and depressive symptoms are not associated with POD.[81]

In conclusion, although the results of the studies published thus far have not consistently identified the aetiology between atherosclerosis in vascular surgery patients and POD, a subgroup of individuals can be identified with clear predictive parameters (smoking and elevated inflammatory markers) for whom a preoperative intervention strategy could be necessary.

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CHAPER 6

STANDARDIZED FRAILTY INDICATOR AS PREDICTOR FOR POSTOPERATIVE DELIRIUM AFTER VASCULAR SURGERY: A PROSPECTIVE COHORT STUDY

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ABSTRACT

Objective

To determine whether the Groningen Frailty Indicator (GFI) has a positive predictive value for post-operative delirium (POD) after vascular surgery.

Materials and Methods

Between March and August 2010, 142 consecutive vascular surgery patients were prospectively evaluated. Preoperatively, the GFI was obtained and post-operatively patients were screened with the Delirium Observation Scale (DOS). Patients with a DOS score ≥ 3 points were assessed by a geriatrician. Delirium was defined by the DSM-IV-TR criteria. Primary outcome variable was the incidence of POD. Secondary outcome variables were any surgical complication and hospital length of stay (HLOS) (≥ 7 days).

Results

Ten patients (7%) developed POD. The highest incidence of POD was found after aortic surgery (17%) and amputation procedures (40%). Increased comorbidities (P= .006), GFI-score (P= .03), renal insufficiency (P= .04), elevated C-reactive protein (P= .008), high American Society of Anaesthesiologists score (P= .05), a DOS score of ≥ 3 points (P= .001), post-operative intensive care unit admittance (P= .01) and HLOS ≥ 7 days (P= .005) were risk factors for POD. The GFI score was not associated with a prolonged HLOS. A mean number of 2 ± 1 (range 0-5) complications were registered. The Receiver operator characteristics (ROC) area under the curve for the GFI was 0.70.

Conclusions

The GFI can be helpful in the early identification of POD after vascular surgery in a select group of high risk patients.

Introduction

Postoperative delirium (POD) is a common and serious complication after surgery. It is defined as an acute disorder of attention and cognition and is characterized by fluctuating symptoms of inattention, disturbance of consciousness and disorganized thinking.[1] Not only does it affect approximately 11-24% of elderly patients on hospital admission, it is also associated with longer hospitalisation and institutionalization, higher medical costs, persistent functional decline and even death.[1-7] With the elderly population increasing at an unprecedented rate, the number of surgical procedures in the elderly will increase in the future. Therefore, the incidence of POD is also likely to increase unless preventive strategies are developed. The first crucial step in delirium prevention is the identification of those patients most at risk for POD. From various studies focussing on POD among surgery patients it is known that vascular surgery patients, especially after aortic surgery, are at highest risk for developing POD.[1] This seems primarily determined by both advanced age and the tendency to have multiple comorbidities, including cerebrovascular disease. Notwithstanding this increased incidence, very few studies focus on risk factors and delirium prevention among vascular surgery patients and an accurate pre-screening tool is currently lacking.[8-12] At the University Medical Centre Groningen, the Groningen Frailty Indicator (GFI) had been developed to identify patients at risk for POD and other adverse outcomes.[13] The GFI is a simple questionnaire consisting of 15 items which are classified in 8 separate groups, consistent with the domains of functioning (Table 1). A score of four or more indicates a higher risk for frailty and possible delirium. Although the GFI has been primarily designed for oncogeriatric surgery patients and has already been validated in various publications and among different patient groups including traumatology, pulmonology, oncology and internal medicine patients, to date the GFI has not been tested among vascular surgery patients.[14-19] The purpose of this prospective cohort study was to determine whether the GFI has a positive predictive value for POD and other surgical complications in vascular surgery patients and could potentially be used as a screening tool to identify patients at high risk for POD.

Table 1. The Groningen Frailty Indicator (GFI)

Event	Yes	No	
Mobility			
Can the patient perform this task without any help? (using tools like walking sticks, wheelchairs or walker is regarded as independent)	0	1	
1. Go shopping	0	1	
2. Walk around outside (around the house or to neighbours)	0	1	
3. Dressing and undressing	0	1	
4. Toilet visit	0	1	
Vision			
5. Does the patient experience problems in daily life by poor vision?	1	0	
Hearing			
6. Does the patient experience problems in daily life by poor hearing?	1	0	
Nutrition			
7. Has the patient involuntarily lost weight (≥6kg) in the past 6 months (or ≥3 kg in one month)	1	0	
Co-morbidity			
8. Does the patient currently use four or more different types of medication?	1	0	
Cognition	**Yes**	**No**	**Sometimes**
9. Does the patient currently has complaints about his memory (or has a history of dementia)	1	0	0
Psychosocial			
10. Does the patient sometimes experience emptiness around him?	1	0	1
11. Does the patient sometimes miss people around him?	1	0	1
12. Does the patient sometimes feel abandoned?	1	0	1
13. Has the patient recently felt sad or depressed?	1	0	1
14. Has the patient recently felt nervous or anxious?	1	0	1
Physical fitness			
15. Which grade would the patient give its physical fitness (0-10, ranging from very bad to good) 0-6=1 7-10= 0	1	0	0
TOTAL SCORE GFI			

A score of four or more indicates a higher risk for frailty and possibly delirium.

Materials and Methods

Between March and August 2010 a total of 142 consecutive vascular surgery patients were prospectively evaluated. All vascular surgery patients admitted and/or operated in an elective setting, regardless of age or comorbidity, were included. All patients were examined both pre- and postoperatively. Preoperatively, the Groningen Frailty Indicator (GFI) was obtained at the surgery outpatient clinic by specially trained nurses. During admission, all patients were observed by nurses trained for this study during three shifts. When POD was high suspected, the ward doctor was informed and further assessment was done by using the delirium observation screening scale (DOS). The DOS consists of 13 items that can be rated as absent or present and describes typical behavioural patterns related to delirium.[20,21] Three or more points were considered indicative for delirium. When delirium was present or suspected a geriatrician was consulted and the diagnosis was confirmed based on the DSM-IV-TR criteria.[22] Medical comorbidity was quantified using the Charlson Comorbidity Index (CCI).[23] As such, each medical condition was assigned a weighted score, range 0-19. Based on these comorbidities the CCI predicts the 1-year mortality. Apart from the GFI and DOS, routine clinical data were recorded pre-, intra- and postoperatively. The following predictors were investigated: preoperative predictors such as age, sex, American Society of Anaesthesiologists score (ASA), haemoglobin level, impaired renal function (glomerular filtration rate (GFR) < 60 ml/min x 1.73 m2), C-reactive protein (CRP), and leukocyte count; intra-operative predictors such as estimated blood loss, type of surgical procedure, and type of anaesthesia; and postoperative predictors and outcomes such as intensive care (ICU) admittance, hospital length of stay (HLOS), psychoactive drug administration (in case of POD) and all medical complications that occurred during hospitalization. Surgical complications and deaths were identified and classified according to a system proposed by Clavien and associates.[24-25] The Clavien-Dindo classification of surgical complications is a validated system that correlates with both the complexity of the procedure as well as HLOS. Complications are graded from 1-6 and range from minor complications without the need for intervention (1) to the death of a patient (6). The primary outcome variable was the incidence of POD. Secondary outcome variables were any (postoperative) surgical complication and HLOS (≥ 7 days). This study was approved by the Institutional Review Board. All patients gave informed consent.

Statistical analyses

Differences between categorical variables that were possibly related to the development of POD were tested with Pearson's χ^2 test (2 variables). Differences between numerical variables were tested with Student's two-tailed test (normally distributed continuous variables) or, if appropriate, Mann-Whitney U test (skewed continuous variables). Skewed continuous variables are shown as median (interquartile range). Variables associated with outcome POD and statistically significant with univariate analysis were entered into multivariate logistic regression analysis using a simultaneous forced entry model (Enter method). We used a probability for stepwise entry of $P < .05$ and a probability of removal of $P < .10$. The GFI was plotted in a receiver operator characteristics (ROC) curve. Two-tail P-values were used throughout and significance was set at $P < .05$. Data are presented as means ± standard deviation, unless stated otherwise. All statistical analyses were done with the Statistical Package for the Social Sciences (SPSS 16.0.1, SPSS; Chicago, ILL, USA, 2007).

Results

A total of 142 patients were included in the study and further analysed. The mean age of the total cohort was 68 ± 11 years (21-87). There was an unequal distribution in sex with 100 men (70%) and 42 women (30%). Patient characteristics and demographic data are shown in table 2. Ten patients (7%) developed POD. The highest incidences were found after open aortic surgery (30%) and amputation procedures (40%). Types of surgery with concomitant POD incidences are shown in Table 3.

Table 2. Patient characteristics and demographic data

Parameter	Number or mean ± SD [a] (Percentage or Range)
Number (%)	142 (100)
Age (years)	68 ± 11 (21-87)
Gender	
Men	100 (70)
Women	42 (30)
Delirium	10 (7.0)
GFI ≥ 4 [b]	50 (35.2)
Comorbidities (CCI) [c]	5 ± 2 (1-14)
Blood loss (ml)	386 ± 802 (0-3500)
Impaired renal function [d]	16 (11)
Pre-operative haemoglobin (mmol/l)	8.4 ± 1.2 (4.7-11.1)
C-reactive protein (mg/l)	5 (5-13)
(median, IQR) [e]	2.6 ± 0.6 (1-4)
ASA [f]	23 (16)
ICU admittance (no of patients)	5.6 ± 4 (1-30)
Hospital length of stay (days)	1.8 ± 1.3 (range 0-5)
Complications [g]	1 (10)

[a] *Standard deviation*

[b] *Groningen Frailty Indicator, a score of four or more indicates a higher risk for frailty and possibly delirium*

[c] *Charlson Comorbidity Index, a weighed index which measures the burden of comorbidities and predicts 1-year mortality (range 0-19 indicating respectively no comorbidities to considerable comorbidities)*

[d] *Defined as glomerular filtration rate (GFR) < 60 ml/min x 1.73 m2*

[e] *CRP level > 5mg/l as measured preoperatively*

[f] *American Society of Anaesthesiologists score (assesses the fitness of patients prior to surgery, 1= a normal healthy patient and 5 = a moribund patient who is not expected to survive without the operation.*

[g] *According to the Clavien-Dindo classification of surgical complications Complications are graded from 1-6 and range from minor complications without the need for intervention (1) to the death of a patient (6).*

Table 3. Types of surgical procedures with concomitant post-operative delirium incidences

Type of procedure	Number of patients (%)	Delirium present (%)
Open aortic surgery	18 (12.7)	3 (30)
Endovascular procedures	30 (21.1)	2 (20)
Peripheral bypass surgery	39 (27.5)	0
Arteriovenous shunt surgery	2 (1.4)	0
Percutaneous interventions	27 (19.0)	0
Amputation surgery	10 (7.0)	4 (40.0)
Miscellaneous	16 (11.3)	1 (10)
Total	142 (100)	10 (100)

Groningen Frailty indicator as predictor for POD

A total of 50 patients (35%) scored a GFI of ≥ 4 points. The predictive value of the GFI was assessed with univariate analyses. A GFI-score ≥ 4 points was significantly related with the development of POD (P=.03). The ROC curve for GFI as predictor for delirium is shown in Figure 1. The area under the curve was 0.70 with the GFI set at ≥ 4 as indicative of an increased risk for POD (sensitivity 50%, specificity 78%). With the GFI cut-off point adjusted to ≥ 6 points, the area under the curve increased to 0.89 (sensitivity 50%, specificity 86%).

Table 4. Univariate analysis with prevalence and median values of risk factors for the development of postoperative delirium

Variable	Predictor available (100%)	Delirium present	Delirium absent	P value [a]
Age (mean±SD)	142	73±10	68±11	.200
Female gender	142	1 (10.0%)	41 (31.1%)	.281
Comorbidities (CCI [b])	142	7.0±2.2	5.0±2.2	.006
Haemoglobin (mg/ml)	107	7.4±1.8	8.5±1.1	.156
Impaired renal function[c]	135	3 (33.3%)	13 (10.3%)	.04
C-reactive protein, median (IQR)	65	5 (5 - 9)	149 (52 - 219)	.008
Leukocyte count	67	11.8±6.1	8.2±2.3	.207
ASA-score > 2 [d]	142	9 (90%)	79 (59%)	.05
Blood loss (ml), median (IQR)	65	350 (13 - 3250)	63 (0 - 188)	.15
Hospital length of stay, median (IQR)	142	10 (6 - 15)	4 (3 - 7)	.005
ICU-admittance	142	4 (44%)	19 (14.1%)	.02
DOS-score > 3 [e]	46	4 (100%)	1 (2.4%)	<. 005
GFI-score, median (IQR) [f]	142	5.5 (2.5-7.5)	3 (1-4)	0.03

Results reported as number

[a] *P-values ≤ 0.05 were considered statistically significant*

[b] *Charlson comorbidity index, a weighed index which measures the burden of comorbidities and predicts 1-year mortality (range 0-19 indicating respectively no comorbidities to considerable comorbidities)*

[c] *Defined as glomerular filtration rate (GFR) < 60 ml/min x 1.73 m2*

[d] *American Society of Anaesthesiologists (assesses the fitness of patients prior to surgery, 1= a normal healthy patient and 5= a moribund patient who is not expected to survive without the operation)*

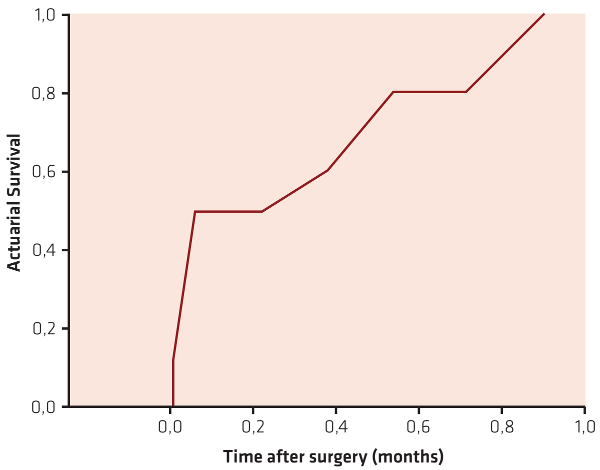
[e] *Delirium Observation Screening scale. Consists of 13 items, ≥ 3 points were considered indicative for delirium.*

[f] *Groningen Frailty Indicator, a score of ≥ 4 indicates higher risk for frailty and possibly delirium.*

IQR= interquartile range

Figure 1.

Receiver operator characteristics (ROC) curve for the GFI as predictor for delirium in 142 patients undergoing elective vascular procedures. The area under the curve is 0.70 with the GFI set at ≥ 4 as indicative of an increased risk for POD (sensitivity 50%, specificity 78%). With a GFI cut-off point of ≥ 6 points, the area under the curve increased to 0.89 (sensitivity 50%, specificity 86%).



Groningen Frailty indicator as predictor for post-operative complications and HLOS

Complications were recorded using the Clavien-Dindo classification. A total of 33 complications were registered (range 0-5). Grades 1 and 2 were most frequently recorded (Table 1). The GFI score was not a predictive factor for the development of complications (P= .83). Also, the number of complications were not significantly related to the development of POD (P= .37). The GFI score was not associated with a prolonged HLOS with a mean HLOS for GFI < 4 of 5.4 ± 3.9 days vs. 5.9 ± 4.2 days for a GFI ≥ 4 (P= .71)

Table 5. Multivariate analysis of risk factors for the development of postoperative delirium.

variable	Odds ratio	95% confidence interval	P value
GFI-score	1.9	0.9-3.7	.05
Comorbidities (CCI [a])	0.9	0.5-1.7	.84
C-reactive protein	1.0	0.9-1.0	.19

[a] *Charlson comorbidity index, a weighed index which measures the burden of comorbidities and predicts 1-year mortality (range 0-19 indicating respectively no comorbidities to considerable comorbidities)*

Additional predictive factors for POD

Univariate analysis yielded various factors that were associated with the development of POD. These factors included the number of comorbidities (P= .006), impaired renal function (glomerular filtration rate (GFR) < 60 ml/min x 1.73 m2) (P= .04), elevated C-reactive protein (CRP) (P= .008), high American Society of Anaesthesiologists (ASA) score (P=.05) and a DOS score of ≥ 3 points (P= < .005). In terms of outcome parameters both post-operative ICU admittance (P= .01) and HLOS ≥ 7 days (P= .005) were associated with the development of POD (Table 4). Although age alone appeared to have no significant relation to POD, high age (> 65 years) did account for > 75% of all complications. Multivariate logistic regression analyses on the factors significantly associated with POD in univariate analyses identified no independent risk factors for POD. However, there was a trend towards statistical significance for the GFI (OR 1.9, 95% CI 0.98-3.77) (Table 5).

Factors and outcome parameters significantly associated with a DOS score of ≥ 3 points were the number of comorbidities (p= .04), increased CRP levels (P= .01) and an extended HLOS ≥ 7 days (P= .02) (Table 6).

Table 6. Univariate analysis with prevalence and median values of risk factors for an increased DOS-score [a]

Variable	Predictor available (100%)	DOS-score < 3	DOS-score ≥ 3	P value [b]
Age	142	69±8.7	74±7.1	.269
Female gender	142	10 (100%)	0 (0%)	.570
Comorbidities (CCI [c])	142	5.1 ±1.9	7.1±1.6	.04
Haemoglobin (mg/ml)	107	8.2±1.0	6.7±1.5	.09
Impaired renal function[d]	135	5 (71.4%)	2 (28.6%)	.173
C-reactive protein, median (IQR)	65	5 (5-11.75)	98 (44-182)	.01
Leukocyte count	67	8.1±2.8	12.9±8.2	.419
ASA-score > 2 [e]	142	27 (78.1%)	4 (12.9%)	.524
Blood loss (ml), median (IQR)	65	87.5 (0-500)	300 (162-1900)	.406
Hospital length of stay, median (IQR)	142	5 (4-7)	8 (7-22)	.017
ICU-admittance	142	6 (75%)	2 (25%)	.158
GFI-score, median (IQR) [f]	142	3 (2-4.5)	3 (1-8.5)	.803

Results reported as number

[a] *Delirium Observation Screening scale. Consists of 13 items, ≥ 3 points were considered indicative for delirium.*

[b] *P-values ≤ 0.05 were considered statistically significant*

[c] *Charlson comorbidity index, a weighed index which measures the burden of comorbidities and predicts 1-year mortality (range 0-19 indicating respectively no comorbidities to considerable comorbidities)*

[d] *Defined as glomerular filtration rate (GFR) < 60 ml/min x 1.73 m2*

[e] *American Society of Anaesthesiologists (assesses the fitness of patients prior to surgery, 1= a normal healthy patient and 5= a moribund patient who is not expected to survive without the operation.)*

[f] *Groningen Frailty Indicator, a score of ≥ 4 indicates higher risk for frailty and possibly delirium.*

IQR= interquartile range

Discussion

This study shows the predictive value of the Groningen Frailty Indicator in the development of postoperative delirium after elective vascular surgery in a heterogeneous patient population. Although many studies have identified risk factors for delirium, this study provides the physician with the ability to be informed about the risk very early in the treatment process. By starting preventive treatments or aggressive assessment during hospitalization in patients with a GFI ≥ 4 points, we believe this could reduce the incidence of POD and perhaps ultimately HLOS. In this context, both the British Geriatric Society and Dutch Professional Guideline have set up useful clinical guidelines to prevent and treat delirium which could be converted to a clinical roadmap and added to the clinical chart of these high risk patients.[26,27] A Cochrane database systematic review on delirium prevention has already proven that both active geriatric consultation and low dose haloperidol medication in high risk postoperative patients may reduce the degree and duration of POD.[28]

In addition to the GFI score, pre-existing comorbidities, an elevated CRP and ICU admittance were associated with an increased risk for POD in univariate analysis. These factors have been reported previously as risk factors for POD and confirm that our studied cohort corresponds with similar studies on POD.[2,7,11,29,30] Contrary to the literature, age was not a predictor for POD in the current study but this may be the result of the limited number of patients in the studied cohort.

There are several drawbacks in this study that need to be addressed. We found an unexpected and relatively low delirium incidence despite the increased awareness and DOS assessment. In the current literature, POD incidences after elective vascular surgery vary from 23 to 39%.[8-12] The reported rate in our study may be low as a result of the increased awareness of signs of POD amongst the nursing staff in the participating wards. It is a known effect that increasing awareness of signs of delirium decreases the incidence of full blown POD. It is however not an uncommon finding that delirium incidence is low in specific prevalence studies. In a large prospective cohort study by Marcantonio et al. postoperative delirium occurred in only 117/1341 (9%) patients older than 50 years, which confirms that the incidence does not entirely dependent on group size.[31] Although we know from several studies focussing on delirium prevention that high age is a risk factor for POD, we included all age groups who underwent elective vascular surgery to reliably estimate the value of the GFI in this cohort of patients. We feel this was a justified choice as the vascular patient in itself is frailer than general surgery patients and thus possibly more prone to develop POD. This has led to a diverse patient population with a mean age of 68 ±11 (range 21-87). Even though the GFI score was not a predictor for postoperative complications, high age (> 65 years) did account for > 75% of all complications. Furthermore, although the GFI seems to provide a good estimate of the risk for POD, it is probably not reliable in a younger (< 65 years) patient group.

In multivariate analyses the problem of underfitting occurred in our model. For a credible risk estimate a ratio of 10 events per independent variable is suggested. Because of the unexpected low POD incidence in our study this ratio could unfortunately not be met in the current model. This means that the outcome for individual variables may not be trustworthy.[32] Consequently, although a trend towards statistical significance was suggested, neither the GFI nor the other independent risk factors reached a significant outcome in the multivariate model.

We would have strongly preferred that all patients had undergone a proper DOS assessment. Unfortunately, because of logistical problems we had to choose the current alternative with DOS assessment only in cases when suspicion for POD was high. This may have led to an underestimation of delirium incidence by missing clinical subtypes such as hypoactive delirium or the unclassified type which account for respectively 29% and 7% of delirium subtypes.[3] Despite the predictive value of the GFI score, the area under the curve was only 0.70 with the GFI score set at ≥ 4 but increased to 0.89 after adjusting the GFI cut-off point to 6 points. Whereas a score of ≥ 4 was chosen for frail patients in general, this cut-off score was determined by previous publications.[14-19] This is the first study in which the GFI score was tested in vascular surgery patients. Within the GFI questionnaire points are given which are consistent with the domains of functioning. Vascular surgery patients are generally considered a group with limited mobility and therefore get points awarded which are not directly related to frailty. It, therefore, may very well be possible that the cut-off score should be adjusted in this patient group. But more likely is that the GFI in its current form may not apply to the entire cohort of patients undergoing vascular surgery. In order to determine its true value in POD risk assessment after vascular surgery, an adjusted score must be used in this specific cohort. In a subsequent study a modified score shall be used which will be applied to the group at highest risk for POD (age ≥ 65 years, aortic surgery and amputation procedures).

In conclusion, this prospective study shows that the GFI, with its limitations, can be helpful in the early identification of a select group of high risk patients with respect to the development of delirium after vascular surgery. Despite a range of publications on pre-and postoperative risk factors for POD, a preoperative tool for risk assessment is not yet at hand. By using the GFI to identify these patients during the preoperative outpatient evaluation, appropriate preventive arrangements, such as preoperative geriatric consultation, can be implemented. In this way HLOS, medical costs and further institutionalization (due to functional loss, loss of independence and the inability to return to there homes) can potentially be reduced. However, the applicability within the entire cohort of vascular surgery patients can be further improved based on this implementation study.

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CHAPER 7

C-REACTIVE PROTEIN PREDICTS POSTOPERATIVE DELIRIUM FOLLOWING VASCULAR SURGERY

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ABSTRACT

Objective

The aetiology of postoperative delirium (POD) following vascular surgery is generally unknown. A possible neuroinflammatory basis for delirium is likely and C-reactive protein (CRP) as a marker for inflammation can possibly play a predictive role.

Materials and Methods

Between March 2010 and September 2011, 277 consecutive elective vascular surgery patients were prospectively evaluated for the development of POD. Various potential risk factors, including postoperative CRP-values, were collected.

Results

The mean age of the patients was 69±11 years (range 21-92). The mean hospital length of stay was 6±4 days (range 1-33). Sixteen patients (6%) developed POD during hospital stay. Univariate analysis revealed multiple comorbidities (P= .001), postoperative elevated CRP levels (P= .001), ICU-admittance (P= .01) and open aortic surgery or amputation procedures (P= .0001) to be significantly related to the development of POD. Multivariate logistic regression analysis confirmed the relationship between an elevated CRP value and POD (OR 1.01, 95% CI 1.00-1.03, P= .04). The sensitivity analyses yielded essentially similar results. Based on the odds ratio, it can be calculated that the risk of POD is increased by approximately 35% if the CRP concentration is 50 mg/L, and by approximately 90% if the CRP concentration is 100 mg/L (compared to a CRP concentration of 5 mg/L). Thirty-one percent (5/16) of patients with POD needed a long stay care facility after discharge (P= .0001).

Conclusions

In this study, CRP predicted POD after vascular surgery. In addition, it was found that POD was associated with a tenfold increase in the need of long stay care after discharge.

Introduction

Postoperative delirium (POD) is defined as an acute disorder of attention and cognition and is characterized by fluctuating symptoms of inattention, disturbance of consciousness and disorganized thinking.[1] Not only does it affect approximately 11-24% of elderly patients during hospital stay, it is also associated with longer hospitalization and institutionalization, higher medical costs, persistent functional decline and even death.[1-7] POD incidences are similar to that of acute myocardial infarction or sepsis making it a serious complication after surgery.[8] The long-term prognosis of POD is largely unknown and underexposed. Nevertheless, there is growing understanding of the fact that POD has major implications on cognitive and functional decline as well as further post-discharge institutionalisation.[5,9] Whereas POD is already a very costly complication, preventing further institutionalisation may render an important contribution in controlling the costs.

The aetiology of POD after vascular surgery is generally unknown, and pre-emptively predicting its occurrence is found to be difficult. Inouye et al. stated that POD is a multifactorial syndrome consisting of a complex interaction of precipitating factors related to surgery and hospitalisation with baseline vulnerabilities.[8,10] Various prevalence studies have identified risk factors for the development of POD, including C-reactive protein (CRP).[11-15] The effect of CRP on postoperative cognition is only partially known. Current data suggest a pathway of inflammation that culminates in higher concentrations of various inflammatory markers in peripheral blood.[16,17] Despite the selective regulation of the blood-brain barrier, the brain is directly influenced by peripheral cytokines through activation of vascular endothelial cells and perivascular cells in the brain. By propagating the inflammatory cascade, this may then lead to neuron injury.[15] This neuroinflammatory response may cause neurocognitive behavioural abnormalities.[18] The aim of this study was to analyze the relationship between CRP and POD in a common vascular surgery population. We hypothesized that elevated CRP values, as a marker for inflammation, are independently associated with POD and that the occurrence of POD increases the need for discharge to a long stay care facility.

Materials and Methods

Design of the study

Between March 2010 and September 2011 a total of 277 consecutive elective vascular surgery patients were prospectively evaluated. All vascular surgery patients admitted and/or operated in an elective setting, regardless of age or comorbidity, were included. Eligible surgical procedures included open and endovascular aortic repair, peripheral bypass surgery, arteriovenous shunt surgery and various percutaneous endovascular interventions. All patients were examined both pre- and postoperatively. All patients gave informed consent.

Postoperative delirium

The primary outcome variable was the incidence of POD. The work up with regard to cognitive and psychosocial assessment has been described in a previous publication by our group.[15] In short, demographic data known to predispose to the development of POD were collected prospectively from the medical records. Clinical awareness was increased by informing the nursing staff on the aims of this study and on the specific signs of POD. A geriatrician was consulted when delirium was present or suspected and the diagnosis was confirmed according to the DSM-IV-TR criteria.[19] Secondary outcomes were hospital length of stay (HLOS) and type of care facility after discharge.

C-reactive protein

CRP values were determined postoperatively on a Roche Modular analyzer (Roche Diagnostics, Almere, The Netherlands). These values were considered elevated when > 5mg/L. Postoperatively the highest value within the first 5 days was recorded for analysis.

Other variables

During admission routine clinical data were recorded pre-, intra- and postoperatively. Preoperatively, the Groningen Frailty Indicator (GFI) was obtained at the surgery outpatient clinic.[15] As pre-operative cognitive impairment and depression are known risk factors for POD, these were also measured. These risk factors were defined by the two items of the GFI and further used for risk assessment for POD in a logistic regression model. The GFI is a simple questionnaire consisting of 15 items, classified in 8 separate groups, consistent with the domains of functioning. The GFI has already been proven to predict POD after vascular surgery.[15] In addition to CRP, the following predictors were investigated; preoperative predictors: age, sex, American Society of Anaesthesiologists score (ASA), haemoglobin level, impaired renal function (estimated glomerular filtration rate (eGFR) < 60 ml/min x 1.73 m2); intra-operative predictors: estimated blood loss, type of surgical procedure, and type of anaesthesia; postoperative predictors: intensive care (ICU) admittance, hospital length of stay (HLOS) and medical complications that occurred during hospitalization. All medical and surgical complications and deaths were identified and classified according to a system proposed by Clavien and associates.[20,21]

Medical comorbidity was quantified using the Charlson Comorbidity Index (CCI).[22] In this index each medical condition was assigned a weighted score, range 0-19. Based on these comorbidities the CCI predicts the 1-year mortality.[23]

Statistical analyses

Normally distributed continuous variables are presented as mean (standard deviation). Skewed continuous variables are shown as median (interquartile range). Differences between numerical variables were tested with Student's two-tailed t-test (normally distributed data) or, if appropriate, Mann-Whitney U test (skewed data). Differences between categorical variables were tested with Pearson's χ^2 test. The association of postoperative delirium (yes/no) with CRP (mg/L) was analysed by logistic regression analysis adjusting for age (years), gender, number of comorbidities, cognitive impairment (yes/no), depression (yes/no), type of procedure (open aortic surgery or amputation vs. other), and ICU admittance (yes/no). In addition, two sensitivity analyses were performed in which we used ASA classification and GFI, respectively, as a measure of comorbidity (instead of the CCI). Two-tailed P-values were used throughout and significance was set at P< 0.05. All statistical analyses were done with the Statistical Package for the Social Sciences (SPSS 16.0.1, SPSS, Chicago, IL, USA, 2007), when appropriate (> 10 patients) confidence intervals were calculated using a method proposed by Altman et al.[24]

Results

This study included 277 patients, 207 men (75%) and 70 women (25%), with a mean age of 69±11 years (range 21-92). Baseline characteristics are listed in Table 1. Operations performed included 13% open aortic surgery (N=36), 26% endovascular procedures (N=74), 31% peripheral bypass surgery (N=85), 15% percutaneous interventions (N=43), 11% amputations (N=30), and 3% miscellaneous (N=9) (Table 1). Postoperatively, 55 patients (20%) were admitted to the intensive care unit (ICU). The mean hospital length of stay was 6 ± 4 days (range 1-33).

Table 1. Patient characteristics and demographic data

Parameter	
Number (%)	277 (100)
Age (years), mean±SD (range)	69±11 (21-92)
Gender, n (%)	
Men	207 (75)
Women	70 (25)
Comorbidities (n)[a], mean±SD	5±2
Impaired renal function[b], n (%)	29 (10)
ASA[c], mean ±SD (range)	3 ±0.5 (1-4)
Type of procedure	
Open aortic surgery, n (%)	36 (13)
Endovascular procedures, n (%)	74 (27)
Peripheral bypass surgery, n (%)	85 (31)
Percutaneous interventions, n (%)	43 (15)
Amputation surgery, n (%)	30 (11)
Miscellaneous, n (%)	9 (3)
Pre-operative haemoglobin (mg/L), mean ±SD (range)	8.8±5.7 (3.6-12.1)
Intra-operative blood loss (ml), median (IQR)	100 (0-500)
ICU admittance, n (%)	55 (20)
Postoperative C-reactive protein (mg/L), median (IQR)	108 (27-188)
Post-operative delirium incidence, n (%)	16 (6)

[a] *Charlson Comorbidity Index, a weighted index which measures the burden of comorbidities and predicts 1-year mortality (range 0-19 indicating respectively no comorbidities to considerable comorbidities)*

[b] *Defined as estimated glomerular filtration rate (eGFR) < 60 ml/min x 1.73 m2*

[c] *American Society of Anaesthesiologists score (assesses the fitness of patients prior to surgery, 1= a normal healthy patient and 5 = a moribund patient who is not expected to survive without the operation.*

Post-operative delirium

Overall, the incidence of post-operative delirium was 6% (Table 2). However, the incidence was highly dependent on the type of surgery. The highest incidence rates (95%CI) were found after open aortic surgery and amputation surgery, 17% (4-29) and 20% (5-35), respectively. The lowest incidence rates (95%CI) were found after endovascular procedures, peripheral bypass surgery and percutaneous interventions, 5% (0-11), 0% (2-13) and 0% (0-8) respectively (Table 2). The mean number of complications (n ± SD) that occurred was equally divided between the POD and non-POD group, respectively 2.1 ± 0.9 and 1.8±1.1, P= .22.

Outcome after discharge was considerably worse in patients with postoperative delirium. Thirty-one percent (95%CI, 14-56%) of patients with POD needed long term care institutionalization after discharge compared to 3% (95%CI, 2-6%) without POD (P= < .005).

Table 2. Risk of post-operative delirium dependent on type of surgical procedure

Type of procedure	**Number of patients**	**Post-operative delirium**		
		Number	**Risk (%)**	**95%CI**
Open aortic surgery	36	6	17%	8% - 32%
Endovascular procedures	74	4	5%	2% - 13%
Peripheral bypass surgery	85	0	0%	0% - 4%
Percutaneous interventions	43	0	0%	0% - 8%
Amputation surgery	30	6	20%	9% - 37%
Miscellaneous	9	0	0%	0% - 30%
Total	277	16	6%	4% - 9%

C-reactive protein and delirium

Univariate analysis revealed multiple comorbidities (P= .001), elevated CRP levels (P= .001), ICU-admittance (P= .01) and open aortic surgery or amputation procedures (P= .0001) to be significantly related to the development of POD. Pre-existing cognitive impairment and depression were significantly associated with the development of POD (P= .006 and P= .02, respectively) (Table 3). Multivariate logistic regression analysis confirmed that an elevated CRP value (OR 1.01, 95% CI 1.0-1.1, P= .04) was the variable most closely correlated with the development of POD. (Table 4) The sensitivity analyses yielded essentially similar results. In the full model, the odds ratio (95%CI) of CRP was 1.01 (1.00-1.02, P= .05) if comorbidity was measured as ASA, and 1.01 (1.00-1.02, P= .03) if comorbidity was measured as GFI. Based on the odds ratio, it can be calculated that the risk of POD is increased by approximately 35% if the CRP concentration is 50 mg/L, and by approximately 90% if the CRP concentration is 100 mg/L (compared to a CRP concentration of 5 mg/L).

Table 3. Univariate analysis of possible risk factors of postoperative delirium

Type of procedure	Delirium present	Delirium absent	P value
Number	16	261	N/A
Age (year), mean±SD	74±9	68±11	.42
Male gender, n (%)	15 (93%)	192 (74%)	.07
Comorbidities[a] (n), mean±SD	6.7±1.8	5.1±1.9	.001
Cognitive impairment, n (%)	3 (19)	19 (7)	.006
Depression, n (%)	10 (62)	123 (47)	.02
ASA-score > 2, n (%)[b]	11 (68%)[d]	147 (56%)[d]	.13
Haemoglobine (mg/L), mean±SD	7.8±1.7	8.9±5.8	.11
Impaired renal function, n (%)[c]	3 (18%)[d]	13 (5%)[d]	.27
CRP (mg/L), median (IQR)	175 (127-246)	89 (24-176)	.001
Open aortic surgery or amputation, n (%)	12(75)	54(21)	< 0.001
Intra-operative blood loss (ml), median (IQR)	350 (0-3000)	100 (0-500)	.40
ICU-admittance, n (%)	7 (43%)	48 (19%)	.01
Complications (n), mean±SD	2.1±0.9	1.8±1.1	.22

[a] *Charlson comorbidity index, a weighted index which measures the burden of comorbidities and predicts 1-year mortality (range 0-19 indicating respectively no comorbidities to considerable comorbidities)*

[b] *American Society of Anesthesiologists (assesses the fitness of patients prior to surgery, 1= a normal healthy patient and 5= a moribund patient who is not expected to survive without the operation).*

[c] *Defined as estimated glomerular filtration rate (eGFR) < 60 ml/min x 1.73 m2*

[d] *Different total number due to missing data.*

Table 4. Multiple logistic regression analysis of the risk of postoperative delirium on CRP.

Variable	Model 1			Model 2			Model 3			Model 4		
	OR	95 % CI	P*	OR	95 % CI	P*	OR	95 % CI	P*	OR	95 % CI	P*
CRP (mg/L)	1.01	1.00-1.11	.003	1.01	1.01-1.02	.02	1.01	1.00-1.04	.007	1.01	1.00-1.03	.04
Age (year)	-			1.05	0.98-1.12	.16	1.04	0.96-1.12	.29	1.05	0.97-1.14	.20
Gender (male vs. female)	-			0.34	0.04-2.83	.32	0.26	0.03-2.24	.22	0.24	0.03-2.33	.22
Comorbidities[a] (n)	-			-			1.12	0.83-1.51	.46	1.10	0.77-1.55	.60
Cognitive impairment[b] (yes vs. no)	-			-			2.86	0.79-10.35	.11	2.91	0.74-11.50	.13
Depression (yes vs. no)	-			-			1.10	0.73-1.65	.66	0.97	0.61-1.53	.90
Type of procedure (open aortic surgery or amputation vs. other)	-			-			-			5.39	1.11-26.26	.04
ICU admittance (yes vs. no)	-			-			-			0.60	0.13-3.25	.65

* *P value*

[a] *Charlson Comorbidity Index*

[b] *As determined by item 9 and 10 of the Groningen Frailty Indicator (GFI).*

Discussion

This study shows that CRP is positively correlated with the development of POD after vascular surgery. This is the first study that not only focuses specifically on the role of CRP and the occurrence of delirium after vascular surgery, but also demonstrates a correlation between the two. Our results further show that this association is independent of known risk factors such as age, pre-existing comorbidity, cognitive impairment and depression or type of surgery. This study also shows that with an increase in CRP level to 100 mg/L, the risk of POD is increased by almost 90%.

In a recent review on the association of atherosclerosis and delirium, inflammation appeared to play a key role in the development of POD, an outcome that is confirmed by this study.[25] A second report, specifically focussing on inflammation in the pathogenesis of delirium within another high risk group, found a similar association between inflammatory processes and the development of delirium.[13]

Although the pathophysiological processes in this process have not yet been fully elucidated, current data suggest a pathway of inflammation that culminates in higher concentrations of various markers in peripheral blood.[13,14] Studies focussing on inflammatory markers as predictor for delirium confirm that patients who developed delirium had significantly elevated levels of interleukins 6 and 8.[26-28] There is increasing evidence that ageing is associated with increased neuroinflammation, manifested as increased levels of activated microglia, the immune cells of the brain.[14] This increased baseline inflammation in the elderly has a priming effect resulting in an enhanced response to peripheral stimuli such as surgery.[29] CRP is an acute-phase protein and a non-specific marker for inflammation, that can give important information and insight in this process and the associated risks. The effect of CRP on outcome appears increasingly important. Two studies on CRP and postoperative outcome showed that an elevated CRP value was independently related with the occurrence of complications as well as an impaired mental status.[13,30] Thus it seems the effect of CRP is much greater than just the occurrence of POD. In vascular surgery it has been shown that CRP is associated with an increased severity of peripheral arterial disease at presentation and independently predicts adverse postoperative events, including cardiovascular, contralateral limb, and graft-related end points after lower extremity bypass surgery.[31] Secondly, it is associated with an increased risk of perioperative myocardial damage and early adverse cardiovascular events in patients undergoing elective vascular surgery.[32] CRP also plays an important role in the composition and progression of atherosclerotic lesions.[33,34] There is growing evidence of a link between plasma CRP and the degree of atherosclerosis suggesting that inhibition of plasma CRP may represent a therapeutic modality for the treatment of cardiovascular disease and possibly POD.[34] The current results support the important role of inflammation after (vascular) surgery and provide the opportunity for a future intervention.

This is the first study that demonstrates the large differences in risk of POD in vascular surgery with the highest incidence rates (95%CI) found after open aortic surgery and amputation surgery An important finding that has not yet been demonstrated to date is the major difference in POD incidence between open and endovascular aortic aneurysm repair

(EVAR). EVAR has become a good alternative to open repair with benefits such as shorter hospitalisation time, less morbidity and 30-day mortality. A lower POD incidence further contributes to these benefits and can be of decisive importance in the treatment of elderly, vulnerable patients.

The occurrence of POD in this study is associated with a statistically significant risk of subsequent long-term care. These findings are in line with the current literature and further emphasize the far-reaching consequences of POD. POD has a poor prognosis when it comes to persistent cognitive decline and increased risk of dementia.[5,35] Frail, elderly patients frequently require discharge to an institutional care facility and this study shows that POD adds a significant contribution to this already increased risk. A systematic review on outcome after POD confirms our results that POD has serious adverse effects on both HLOS and institutionalisation.[35]

The level of CRP may be related to the number or severity of complications. It also has been shown that the occurrence of complications is a potential risk factor for POD. With an equally divided mean number of complications between the POD and non-POD group, it seems unlikely that this has influenced the outcome.

This study has some limitations. As in our previous publication on POD after vascular surgery, the incidence of delirium is much lower than reported in the literature. Therefore we were limited in the number of variables in our multiple logistic regression analysis. However, the incidence in our study was also strongly dependent on the type of surgery, resulting in a large variance between the various operations. The incidence rate in our study was comparable to the incidence rates in large prospective studies and it is generally acknowledged that large studies yield the most reliable estimates.[36, 37] In a large prospective cohort study by Marcantonio et al. POD occurred in only 117/1341 (9%) patients older than 50 years.[36] The same goes for a large international study by Rudolph et al. in which a large group of patients were daily assessed for delirium after non-cardiac surgery.[37] Again, only 8% of patients developed POD. So although we describe a "high risk" group, a relatively low POD incidence is not uncommon. Proactive geriatric consultation has been proven to reduce both delirium incidence and severity after surgery and, as it is readily available in our hospital, this could have led a low delirium incidence.[38,39]

Pre-operative cognitive impairment and depression are known risk factors for the occurrence of POD.[40] In this study we corrected for these variables by making use of 2 items of the GFI. By the use of these sub-groups one can easily correct for two important risk factors. Futhermore, clinical subtypes such as hypoactive delirium or the unclassified type which account for respectively 29% and 7% of delirium subtypes could have been missed, thus leading to an underestimation of the POD incidence.[41] However, the clinical relevance of these subtypes remains questionable and usually, they have no therapeutical consequences.

Although CRP alone is not sufficient as a target for prevention in a multifactorial disease as POD, evidence is growing of (neuro-)inflammation as a common final pathway in the development of POD. This study adds relevant information to the growing understanding of this pathway. However, in this process, there are several factors which influence the onset of POD and there is certainly a balance between the degree of neuroinflammation and the vulnerability of the patient. Multivariate models, such as proposed by Böhner et al., are needed to truly predict POD and develop preventive strategies.[42] Their model also showed CRP to be significantly associated with POD, but unfortunately, this high quality prospective study, failed to further explore this unexpected outcome. Further research may strengthen the relationship between CRP and POD and may as well provide better insights into its etiology.

In conclusion, elevated CRP levels, as a measure of inflammation, should be considered a risk factor for the development of POD and CRP should therefore be determined for each patient prior to surgery. The occurrence of POD has major implications for the subsequent care facility after discharge. Patients with elevated CRP values are eligible for active geriatric consultation given the risk of POD and subsequently the need for post-discharge institutionalisation.

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SECTION III

CHAPER 8

SUMMARY, GENERAL DISCUSSION AND FUTURE PERSPECTIVES

Life expectancy in the western world is increasing dramatically, and as a result the population is expanding and getting older. The elderly are a growing surgical population with more comorbidities and less physiological reserve compared with nonelderly patients. Subsequently, we are increasingly confronted with the specialized care that elderly patients require. Although advances in medical care have greatly contributed to improved outcomes in this vulnerable group, age dependent factors remain that still need attention. This increased vulnerability is frequently referred to as frail, which is defined as the risk for adverse outcomes due to losses in different domains of functioning, related directly to these adverse processes.[1] Although this applies to both general medicine and surgery, when considering surgery in this patient population these factors weigh most heavily. The vulnerability of this group means that adjusting to changes in stress, physiology and environment will have a much greater impact. That in turn leads to a greater risk of complications and higher morbidity and mortality. In the past this increased risk may have resulted in a deliberate or subconscious bias towards a conservative approach in elderly patients.

In surgery, vascular surgery patients are above the parapet when it comes to frailty and vulnerability.[2] Most obviously this seems to be caused by the fact that vascular patients are old and usually present with multiple comorbidities, including cerebrovascular disease.

For elderly vascular surgery patients admitted to the hospital this means that specific attention should be focused and targeted on this increased vulnerability. Although there is a lively discussion regarding the treatment of octogenarians, recent studies have shown that octogenarians not only have a very good survival after major (vascular) surgery, there are no significant differences in outcome and/or complications compared to a younger patient cohort.[3-9] A conservative approach based on age alone therefore seems no longer justified.
In this thesis we have looked on several levels at the outcome of vascular surgery procedures in octogenarians. We hypothesized that octogenarians could be treated safely, or at least as safe as a younger patient cohort. Based on these results we have focused on several crucial parameters that either positively or negatively influenced the outcome. Where possible we have looked at potential preventive measures, both in the literature as in additional studies. On this basis we postulated potential targets for intervention.

In **Chapter 2** we investigated whether advanced age may be a reason to refrain from full treatment in patients with an acute abdominal aortic aneurysm (AAAA). When dealing with octogenarians who present with an AAAA, the balance between surgical risk, late-term survival and quality of live are important items which weigh heavily in the final decision. Secondly, with current budget restraints, one may bring up treatment of AAAA and subsequent ICU admission in the elderly patient for discussion. The purpose of this study was to investigate whether this holds true for octogenarians suffering from AAAA. During a period of 8 years a total of 290 consecutive patients with manifest AAAA were presented at our hospital, of whom 46 (16%) were older or equal to 80 years. At the regional level we have an integrated system for the rapid transport and immediate treatment of AAAA. Our strategy was to treat all patients unless they had a very poor performance score (Karnofsky performance score ≤ 40).

One-year actuarial survival for all patients was 71%. After two and five years, these numbers were 67% and 57%, respectively. Kaplan Meier survival analysis revealed a significantly better survival for the younger patients. Two-year actuarial survival was 70% for patients younger than 80 and 52% for those older than 80. At five years follow-up, these figures were 62% and 29%, respectively. Mean survival in patients older than 80 was still 39.8 ± 6.8 months. Overall mortality for AAAA was 37% (58/152) for patients younger than 80 and 55% (22/37) for patients older than 80 years (P= .02). But perhaps just as important, no statistical differences were observed in complications between the younger and older group. So after such a disastrous event as AAAA, a median survival of more than 2.8 years can be achieved in octogenarians, while ICU and hospital length of stay is not prolonged compared to younger patients. And with certain death in absence of treatment we feel that waiving a treatment no longer seems justified. Although Quality of life (QoL) in this study was defined as complications interfering with the activities of daily living (ADL), this gives no real and/or reliable representation of the actual QoL. In addition, we looked at the 30-day outcome and quality of life after elective endovascular abdominal aortic aneurysm repair in octogenarians. The results of this analysis are outlined in **Chapter 3**. Using the Endurant Stent Graft Natural Selection Global Postmarket Registry (ENGAGE), a multicentre, non-interventional, non-randomized, single-arm prospective study, we hypothesized that octogenarians may be safely treated with EVAR while still providing acceptable post-procedure quality of life. Again, patients were divided in two groups; those aged ≥ 80 years (274, 22.8%) and those < 80 years (926, 71.2%). Quality of life was assessed using the EuroQoL 5 -Dimensions Questionnaire (EQ-5D) index score. While the primary indication for stent graft placement was similar in both groups, octogenarians had a significantly higher ASA classification and the younger cohort was more likely to smoke and consume alcohol. Although octogenarians had a slightly larger aneurysms (P= .010) and greater average infrarenal neck angulation (P= .010), there was no difference in the number of secondary endovascular procedures or conversion to open surgery between the groups. Also, 30-day all-cause mortality was comparable between the two groups. In terms of QoL, octogenarians scored themselves lower than younger patients in the dimensions of baseline mobility and self-care.

At discharge, both groups scored themselves lower in all health status dimensions compared with their preoperative baseline, except for anxiety/depression which was improved over baseline in the younger group (P< .001). Compared with younger patients, octogenarians had decreased self-care perceptions at discharge (P= .041). The discharge health state and composite EQ-5D were not significantly different in either the octogenarians or younger group. At 30 days after operation, the octogenarian group had persistent decreases in the usual activities dimension compared with preoperative baseline (P= .010). The younger patients had lessened anxiety/depression vs. their baseline, while the octogenarian group did not display a similar level of improvement in this dimension Compared with younger patients, the octogenarians had a lower composite EQ-5D index (P= .003) and they scored themselves lower in the mobility (P<0.001) and self-care (P<0.001) dimensions at 30 days when compared with the younger group. By contrast, the composite EQ-5D index, while similar in the two groups at baseline and at discharge, was significantly lower in octogenarians than younger patients at 30 days (P= .003), suggesting that recovery of quality of life measured appeared to occur sooner in those patients below age 80.

In the above studies, we deliberately choose the outcome after abdominal aneurysm repair and both acute and elective. Not only is this a common problem in vascular surgery, the outcome is often associated with high morbidity and mortality. It is precisely this risk that elderly patients are often considered unsuitable. However, both studies show that these vulnerable patients can be treated with excellent results. The same arguments are often cited when dealing with carotid stenosis in octogenarians. In **Chapter 4** we focused on carotid endarterectomy (CEA) and have tried to evaluate the outcome of CEA in octogenarians. This is an important and topical subject because in the past advanced age has been associated with an increased risk for complications after CEA. Following this, elderly patients were frequently offered replacement therapy by CAS as a less invasive alternative, even though both a sub analysis of the SPACE study and a recent meta-analysis of the three major randomized controlled trials between CEA and CAS, age (≥ 70 years) significantly modified the treatment effect in favour of CEA. A total of 548 patients, undergoing carotid artery revascularization by means of CEA, were analyzed from a prospectively recorded vascular registry. Patients were divided in two groups aged ≥ 80 years (71, 13%) and those < 80 years (477, 87%). Primary outcome measures were mortality, any stroke (major or minor), post-procedural complications and HLOS. At baseline octogenarians differed significantly, in terms of symptomatology, in the number of ischemic strokes compared to the younger cohort (resp. 48% vs. 38%). No statistical differences were observed regarding major/minor stroke, TIA or other post-procedural complications between the two cohorts. Octogenarians however did tend have a longer HLOS (P= .0001) and developed POD much more frequent compared to patients aged < 80 years (P< .0001). Thus we conclude that octogenarians who suffer from carotid artery stenosis can be safely treated by CEA.

This difference in occurrence of POD is not uncommon. However, the reason why vascular surgery patients have such a high risk is grounds for much debate. We wondered whether atherosclerosis itself may be the cause of this increased risk. In **Chapter 5** we present a review where we look at the existence of a potential relationship between atherosclerosis and the occurrence of POD in vascular surgery patients. And although we could not consistently determine the origin between atherosclerosis in vascular surgery patients and POD, we did identify two predictive parameters, i.e. smoking and elevated inflammatory markers, which may lead to preoperative intervention strategies.

Unfortunately very few studies focus on risk factors and POD prevention among vascular surgery patients and an accurate pre-screening tool is currently lacking. Although specialized geriatric wards and multicomponent interventions have been proven to prevent POD and improve outcome, in many hospitals this is probably not feasible. Within this framework we have designed a prospective study, where we tested the Groningen Frailty Indicator (GFI) whether it had a positive predictive value for (POD) after vascular surgery. These results are described in **Chapter 6**. The GFI has been developed to screens for diminished abilities and resources in physical, cognitive, social and psychological functioning. It consists of a simple questionnaire consisting of 15 items which are classified in 8 separate groups, consistent with the domains of functioning. A GFI score of ≥ 4 was chosen, a cut-off score which was determined by previous publications. It turned out that the GFI was significantly related with the development of POD (P= .03), with an area under the curve of 0.70 (sensitivity 50%, specificity 78%). These results could provide the physician with the ability to be

informed about the risk very early in the treatment process. Whether preventive strategies or aggressive assessment could reduce the incidence of POD can, based on these results, not be concluded and will need further research. Interestingly, various other factors, such as increased comorbidities, renal insufficiency, elevated C-reactive protein, high American Society of Anaesthesiologists score, a DOS score of ≥ 3 points, post-operative intensive care unit admittance and HLOS ≥ 7 days were significantly associated with POD. Of these factors we were particularly interested in the elevated CRP. Although not an uncommon finding, there are few theories that discuss the possible aetiology.[10-15] What we do know is that the brain is directly influenced by peripheral cytokines through activation of vascular endothelial cells and perivascular cells in the brain. By propagating the inflammatory cascade, this may then lead to neuron injury. One of the studies focusing on CRP and activation of vascular endothelial cells found a close correlation between the two systems, further supporting the concept of vascular cell activation by inflammatory processes[16]. In **Chapter 7** we extended the analysis on CRP and further investigated the association with POD in our cohort. This study included 277 consecutive vascular surgery patients admitted and/or operated in an elective setting, regardless of age or comorbidity. Sixteen patients (6%) developed POD during the hospital admission. Operations performed included 13% open aortic surgery (N=36), 26% endovascular procedures (N=74), 31% peripheral bypass surgery (N=85), 15% percutaneous interventions (N=43), 11% amputations (N=30), and 3% miscellaneous (N=9) Overall, the incidence of post-operative delirium was 6%. However, the incidence was highly dependent on the type of surgery. The highest incidence rates (95%CI) were found after open aortic surgery and amputation surgery, 17% (4-29) and 20% (5-35), respectively. Outcome after discharge was considerably worse in patients with postoperative delirium. Thirty-one percent (95%CI, 14-56%) of patients with POD needed long term care institutionalization after discharge compared to 3% (95%CI, 2-6%) without POD (P= .0001).

Univariate analysis revealed multiple comorbidities, elevated CRP levels, ICU-admittance and open aortic surgery or amputation procedures to be significantly related to the development of POD. Pre-existing cognitive impairment and depression were significantly associated with the development of POD. Multivariate logistic regression analysis confirmed that an elevated CRP value was the variable most closely correlated with the development of POD. The sensitivity analyses yielded essentially similar results. Based on the odds ratio, it can be calculated that the risk of POD is increased by approximately 35% if the CRP concentration is 50 mg/L, and by approximately 90% if the CRP concentration is 100 mg/L (compared to a CRP concentration of 5 mg/L).

This study showed not only that determining the patients CRP value can give important information on POD risk, but also that POD is associated with a high risk of subsequent long-term care. This further emphasizes the far-reaching consequences of POD and the improvement that can be achieved in the prevention of POD.

Discussion

This thesis shows that elderly patients are suitable to undergo vascular surgery. Although clear risk factors have been determined, particularly with regard to the occurrence of POD, it seems safe to operate this vulnerable group. However, one important question remains unanswered. In this thesis we have not examined the cost effectiveness of treating older patients. In an era of financial uncertainty and crisis, it is not inconceivable that restrictions are imposed, both in terms of hospitalization and surgery costs.

By the age of 80 years, the likelihood of having a surgical procedure is 35.3%. Patients subjected to surgery have a higher adjusted mean number of hospital admissions compared to those admitted to hospital without a surgical procedure and have almost twice as many days in intensive care.[17] This has an enormous impact on medical costs and resources. Although to date this has only been investigated following hip fracture surgery, comorbidities significantly affect the cost of hospitalization and length of stay.[18] It seems only logical that these results can be extended to vascular surgery patients, hence this is a group known for its comorbid illnesses. What we do already know is that there are high costs associated with vascular-related hospitalizations and high rates of rehospitalization and associated costs for patients with peripheral arterial disease.[19] Even though this thesis describes good results after EVAR, one can also raise questions on costs and benefit. With the current climate of cost containment and limited reimbursement for health-care delivery, a critical analysis of the costs versus its relative benefits seems important. And certainly when treating octogenarians, where median survival remains limited by the natural life expectancy. Current literature clearly show that EVAR is appreciably more expensive compared to open repair. Also, the decreased ICU and HLOS do not compensate for the cost of EVAR.[20] With the proposed reductions in reimbursement; the ability to cover the cost may be threatened. Because long-term surveillance is considered mandatory after EVAR, the follow-up costs will further increase the cost disparity between EVAR and open repair.[21]

In **Chapter 4** the differences between CAS and CEA in octogenarians have been extensively discussed. But besides the outcome of each treatment, there are also great differences in cost that should be considered. Cost analysis indicates substantially higher total and direct costs associated with CAS compared with CEA. This difference appears to be particularly related to the expensive procedure-related materials.[22] The cost of carotid revascularisation in the elderly is already significantly greater than that for younger patients due to a greater number of major complications in the elderly group.[23] Recently a large comparative effectiveness analysis on carotid revascularization stratified by age further concluded that the widespread use of CAS in elderly patients should be discouraged due to inferior 30-day outcomes.[24] And with these high costs in mind, CAS seems to have no role in treating octogenarians with carotid stenosis.

In the United States the surgical intensity at the end of life is related to the number of hospital beds per head.[17] The Netherlands has 3 hospital beds per 1000 inhabitants. It is expected that by 2015 this will have dropped to 2 per 1000 inhabitants.[25] This will lead to capacity constraints and priorities will probably need to be set. This means that this decrease will have adverse effects for the treatment of elderly patients, provided that the same trend is

followed as in the USA. But when there are choices to be made with respect to age then were is the border? Gradually more and more articles appear that show good results of treatment of nonagenarians. But whether a life expectancy of 1-2 years outweighs the growing financial constraints of our healthcare is now decided on an individual basis. By better techniques and patient care, octo- and nonagenarians will increasingly appear suitable for (major) surgery. In the future, however, comparative effectiveness and cost-benefit evaluation will probably play an increasingly important role. And if the costs of EVAR will not go down its future is uncertain for elderly patients.

Future perspectives

This thesis describes the first steps in treating elderly patients in vascular surgery. Although this study shows that this fragile group can be treated with excellent results, more studies are needed to further confirm these results. Despite the steady increase of elderly patients few studies examined the effects of age on treatment outcome in this increasingly important patient group. In future randomized controlled trials elderly patients should no longer be excluded. Many elderly patients become part of the general medical population in the next decade. Results of major studies should therefore also apply on the elderly to supports medical decision-making in this difficult patient category. In the current global uncertain financial state comparative effectiveness research and cost-benefit evaluation will be increasingly important. Since the introduction of EVAR the price of grafts has increased substantially. We should be mindful of not only the efficacy of any technology, but also its cost.

Regarding treatment and prevention of POD we are still in its infancy. Although the aetiology is becoming more clearly, the real gain lies in preventing its occurrence. With the lack of a good alternative, the GFI may play a role in the near future but needs to be further developed for vascular surgery patients. With an adjusted score and an appropriate preoperative intervention plan there is much to gain. These issues will have our attention in the future and will hopefully contribute to safer and more efficient treatment of elderly patients.

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CHAPER 9

SUMMARY IN DUTCH/ NEDERLANDSE SAMENVATTING

De levensverwachting in de westerse wereld is afgelopen decennia dramatisch gestegen met als gevolg dat de bevolking niet alleen toeneemt maar ook ouder wordt. Deze ouderen vormen een groeiende chirurgische populatie met meer comorbiditeit en een verminderde fysiologische reserve in vergelijking met jonge patiënten. Hierdoor worden we steeds vaker geconfronteerd met de gespecialiseerde zorg die ouderen nodig hebben. Hoewel vooruitgang in de medische zorg veel heeft bijgedragen aan de huidige goede resultaten, blijven er specifieke leeftijdsafhankelijke factoren die nog steeds onze aandacht behoeven. Deze verhoogde kwetsbaarheid geeft een verhoogd risico op een slechtere uitkomst door verlies in het basis functioneren.[1] En hoewel dit geldt voor zowel de algemene geneeskunde als de chirurgie, bij het overwegen van chirurgie in deze patiënten groep wegen deze factoren extra zwaar. De verhoogde kwetsbaarheid van deze groep betekend dat aanpassing aan veranderingen in stress, fysiologie en hun omgeving een veel grotere impact zal hebben. Hierdoor lopen zij een groter risico op een hogere morbiditeit en mortaliteit. In het verleden kan dit verhoogde risico hebben geleid tot een bewuste of onbewuste voorkeur voor een conservatieve benadering bij oudere patiënten.

Binnen de chirurgie steekt de vaatchirurgie ruim boven het maaiveld uit als het gaat zwakke en kwetsbare patiënten.[2] Meest waarschijnlijk berust dit op het feit dat vaatpatiënten vaak ouder zijn en multipele comorbiditeiten hebben zoals hypertensie, diabetes mellitus en cerebrovasculaire vaatlijden.

Voor de oudere vaatchirurgische patiënt betekend opname in het ziekenhuis dat er specifieke aandacht moet worden besteed aan deze verhoogde kwetsbaarheid. En hoewel men af en toe nog terughoudend kan zijn in de behandeling van bv. patiënten ≥ 80 jaar laten diverse studies zien dat de overleving na majeure (vaat)chirurgie boven verwachting goed is en niet onder doet aan die van jongere patienten.[3-9] Hierdoor lijkt het niet langer verantwoord om alleen op basis van leeftijd patiënten enkel nog conservatief te behandelen.

In dit proefschrift hebben we gekeken naar de resultaten van diverse vaatchirurgische procedures in patiënten ≥ 80 jaar. Onze hypothese was dat oudere patiënten veilig, of tenminste net zo veilig, konden worden behandeld als een jongere patiëntenpopulatie. Op basis van deze resultaten hebben we ons gericht op de meest cruciale parameters die zowel positief als negatief de uitkomst kunnen hebben beïnvloed.

In **hoofdstuk 2** hebben we gekeken naar de uitkomsten van een acuut abdominaal aorta aneurysma (AAAA) en beoordeeld of een gevorderde leeftijd een reden kan zijn om af te zien van een volledige behandeling met operatieve correctie en aansluitend een intensive care opname. Bij de behandeling van tachtigjarigen die zich presenteren met een AAAA zijn de balans tussen het chirurgisch risico, de lange-termijns overleving en de kwaliteit van leven belangrijke onderwerpen die zwaar wegen in de discussie. Tevens kan de hele behandeling van tachtigjarigen, in een periode van financiële onzekerheid en bezuinigingen, ter discussie worden gesteld. Het doel van deze studie was om te onderzoeken of dit daadwerkelijk valide argumenten zijn voor tachtigjarigen die zich presenteren met een AAAA. Gedurende een periode van 8 jaar presenteerde zich 290 opeenvolgende patiënten in ons ziekenhuis met een AAAA, waarvan er 46 (16%) ≥ 80 jaar waren. Op regionaal niveau hebben wij een geïntegreerd systeem voor het snelle transport en de onmiddellijke behandeling van patiënten met een AAAA. Onze strategie was om in principe alle patiënten te behandelen, tenzij ze primair in een zeer slechte conditie verkeerden (bv. Karnofsky score ≤ 40).

Patiënten ≥80 jaar verbleven langer op de intensive care (IC) in vergelijking met jonge patiënten. Kaplan Meier analyse liet een significant betere overleving zien voor de jongere patiënten. De twee jaars actuariële overleving was 70% voor patiënten jonger dan 80 jaar en 52% voor patiënten ouder dan 80 jaar. Na vijf jaar follow-up waren deze cijfers 62% en 29% respectievelijk. De gemiddelde overleving bij patiënten ouder dan 80 jaar was opvallend genoeg nog 39.8 ± 6.8 maanden. De totale mortaliteit voor AAAA was 37% (58/152) voor patiënten jonger dan 80 jaar en 55% (22/37) voor patiënten ouder dan 80 jaar (P= .02). Maar even belangrijk, er werden geen statistisch verschillen waargenomen in complicaties tussen de jongere en oudere groep. Dus na een rampzalige gebeurtenis als AAAA kan een mediane overleving van meer dan 2,8 jaar worden bereikt in patiënten ouder dan 80 jaar, terwijl opnameduur en risico op complicaties niet anders zijn dan bij jongere patiënten. En met een zekere dood zonder behandeling lijkt afzien van een behandeling niet langer gerechtvaardigd. Hoewel kwaliteit van leven (KvL) in deze studie werd gedefinieerd als complicaties die ingrijpen in de dagelijkse activiteiten, geeft dit geen echte en/of betrouwbare weergave van het werkelijk effect op de KvL. In aanvulling hierop hebben we gekeken naar de 30-dagen resultaten en de KvL na electieve endovasculaire aneurysma uitschakeling in tachtigjarigen. De resultaten van deze studie worden beschreven in **hoofdstuk 3**. Met behulp van de Endurant Stent Graft Natural Selection Global Postmarket Registry (ENGAGE), een multicenter, niet-gerandomiseerde, prospectieve studie, hebben we de hypothese opgesteld dat patiënten ouder dan 80 jaar veilig kunnen worden behandeld met behoud van een goede KvL. Ook hier werden de patiënten verdeeld in twee groepen; patiënten ≥ 80 jaar (274, 22.8%) en < 80 jaar (926, 71.2%). Kvl werd gemeten met de EuroQoL 5-Dimensions vragenlijst (EQ-5D). Hoewel de primaire indicatie voor stengraft plaatsing vergelijkbaar was in beide groepen hadden patiënten ouder dan 80 jaar een significant hogere ASA classificatie rookte het jongere cohort meer tabak en dronken zij vaker alcohol. Behoudens iets grotere aneurysmata (P= .010) en een steilere aneurysma nek (P= .010) in de groep van 80 jaar en ouder, was er geen verschil in het aantal secundaire interventies of conversies naar een open procedure tussen de beide groepen. De 30-dagen mortaliteit was eveneens vergelijkbaar tussen de twee groepen (P= .119). Ten aanzien van KvL scoorde patiënten ≥ 80 jaar zich, bij aanvang van de studie, lager in de dimensies mobiliteit en zelfzorg. Bij ontslag scoorden beide groepen zichzelf lager in alle gezondheid dimensies ten opzichte van hun baseline, met uitzondering van angst en depressie die ten opzichte van de baseline was verbeterd in de jongere groep (P< .001). In vergelijking met jongere patiënten hadden patiënten ≥ 80 jaar een verminderd gevoel van zelfzorg bij ontslag (P= .041). De overige gezondheidstoestand en EQ-5D waren niet significant verschillend tussen beide groepen. Na 30 dagen was er nog steeds sprake van een persisterende daling in de dagelijkse activiteiten ten opzichte van de baseline waarde (P= .010). Hoewel de jongere patiënten een sterk afgenomen gevoel van angst/depressie ervaarden (P< .001) bleef deze verbetering uit in de groep ≥ 80 jaar (P= .746). In vergelijking met de jongere patiënten scoorden de groep ≥ 80 jaar na 30 dagen een lagere EQ-5D index (P= .003) en scoorden ze zich lager in mobiliteit en zelfzorg. Echter, terwijl de EQ-5D index vergelijkbaar was in beide groepen bij aanvang van de studie en bij ontslag, was dit significant lager in de groep ≥ 80 jaar (P= .003), wat suggereert dat herstel van KvL langer duurt bij de oudere patiënten.

In bovengenoemde studies we bewust gekeken naar de uitkomst na abdominal aneurysma herstel en zowel in acute als electieve setting. Dit is namelijk niet alleen een veel voorkomend probleem binnen de vaatchirurgie, maar de uitkomst gaat vaak gepaard met een hoge morbiditeit en mortaliteit. En het is juist dit risico waardoor oudere patienten vaak ongeschikt worden bevonden voor chirurgie. Echter, beide studies laten zien dat deze kwetsbare patienten uitstekend behandeld kunnen worden. Dezelfde argumenten worden vaak genoemd voor oudere patienten met een carotis stenose. Daarom hebben we in **hoofdstuk 4** ons gericht op de carotis endarteriectomie (CEA) en hebben geprobeerd om de uitkomst van de CEA in tachtigjarigen te evalueren. Dit is een belangrijk en actueel onderwerp want in het verleden werd leeftijd in verband gebracht met een verhoogd risico op complicaties na CEA. Naar aanleiding hiervan werd oudere patiënten, vaak als vervangende therapie, carotis stenting (CAS) aangeboden als zijnde een minder invasief, en daardoor veiliger, alternatief. En dat terwijl een subanalyse van de SPACE trial en een recente meta-analyse van de drie grote gerandomiseerde studies tussen CEA en CAS laten zien dat CAS een significant effect heeft op de behandel uitkomst in het voordeel van CEA.

In onze studie werden 548 patiënten, die carotis revascularisatie hebben ondergaan door middels van CEA, geanalyseerd vanuit een prospectieve database. Patiënten werden verdeeld in twee leeftijd groepen, namelijk < 80 jaar (71, 13%) en ≥ 80 jaar (477, 87%). De primaire uitkomstmaten waren overlijden, een beroerte (groot of klein), postoperatieve complicaties en ziekenhuis opnameduur. Patiënten ≥ 80 jaar hadden significant vaker preoperatief een herseninfarct doorgemaakt, in vergelijking met de jonger cohort (resp. 48% vs. 38%). Postoperatief werden geen statistische verschillen waargenomen ten aanzien van het aantal infarcten, TIA's of andere postprocedurele complicaties tussen de twee groepen. Patiënten ≥ 80 jaar hadden wel een significant langere opnameduur (P= .0001) en ontwikkelden vaker een postoperatief delier (POD) (P< .0001) in vergelijking met patiënten < 80 jaar.

Dit verschil in optreden van POD is niet ongebruikelijk. Echter, de reden waarom oudere vaatchirurgische patiënten een zo hoog risico hebben is reden voor veel discussie. Hoewel er veel hypothesen bestaan stelden wij ons de vraag of atherosclerose zelf een oorzaak kan zijn voor dit verhoogde risico. Om deze vraag te kunnen beantwoorden hebben wij in **hoofdstuk 5** een review geschreven waarin gekeken werd naar het bestaan van een mogelijke relatie tussen atherosclerose en het ontstaan van POD in vaatchirurgische patiënten. En hoewel geen heel duidelijke relatie kon worden vastgesteld tussen atherosclerose, vaatchirurgie en POD, identificeerden wij wel de 2 voorspellende parameters roken en verhoogde inflammatoire markers die zouden kunnen leiden tot interventiestrategieën. Jammer genoeg zijn er maar weinig studies die zich richten op risicofactoren en POD preventie onder vaatchirurgische patiënten. Daardoor bestaat er tot op heden nog geen nauwkeurige test die preoperatief een risico inschatting kan maken op het optrden van POD. Hoewel gespecialiseerde geriatrische afdelingen en multicomponent interventies aangetoond hebben POD te voorkomen is dit in veel ziekenhuizen waarschijnlijk niet haalbaar. In dit kader hebben wij een prospectieve studie ontworpen waarin de Groningen Frailty Indicator (GFI) werd getest of deze een positief voorspellende waarde heeft voor het optreden van POD na vaatchirurgie. De resultaten van deze studie worden beschreven **hoofdstuk 6**. De GFI is ooit ontwikkeld om patiënten te identificeren met een bepaalde kwetsbaarheid op basis van een verminderd fysieke, cognitieve, sociaal en psychologisch functioneren. Deze domeinen lijken overeen te komen met risicofactoren voor POD. De GFI bestaat uit een eenvoudige vragenlijst bestaande uit 15 onderdelen die in 8 afzonderlijke groepen in overeenstemming zijn met de domeinen van het functioneren. Een GFI score van ≥ 4 werd gekozen als afkap punt op basis van eerdere publicaties. In deze studie bleek de GFI een significante relatie te hebben met het optreden van POD (P=0.03), met een ROC oppervlakte onder de curve van 0.70 (sensitiviteit 50%, specificiteit 78%). Deze eenvoudig te bepalen score biedt een behandelend specialist de mogelijkheid om vroeg in het behandelingsproces geïnformeerd te zijn over het risico op POD en hier zo nodig naar te handelen. Of preventieve maatregelen en empirische strategieën het optreden van POD daadwerkelijk beïnvloeden, kan op basis van deze resultaten niet worden geconcludeerd en verder onderzoek is dan ook noodzakelijk. Interessant is dat verschillende andere factoren, zoals een toename in comorbiditeit, nierinsufficiëntie, verhoogd C-reactive protein (CRP), een hoge American Society of Anaesthesiologists score (ASA), een DOS score van ≥ 3 punten, postoperatieve intensive care opname en een ziekenhuisopname duur ≥ 7 dagen significant waren geassocieerd met POD. Van deze factoren waren wij vooral geïnteresseerd in de verhoogde CRP waarden als risico factor. Hoewel dit geen onbekende bevinding is, zijn er maar weinig theorieën die over een mogelijke etiologie spreken.[10-15] Wat we wel weten is dat de hersenen direct worden beïnvloed door perifere cytokines door activatie van de vasculaire endotheliale cellen en perivasculaire cellen in de hersenen. Door activatie van deze inflammatoire cascade kan dit leiden tot zenuwschade in de hersenen. Een van de studies die zich specifiek heeft gericht op CRP en activering van de vasculaire endotheliale cellen vond een nauwe correlatie tussen de twee systemen, een uitkomst die bovenstaand concept alleen maar verder ondersteund.[16]

In **hoofdstuk 7** hebben wij binnen een prospectief cohort verder gekeken naar de associatie van CRP en POD in vaatchirurgische patiënten. Hierbij hebben we de analyse tussen CRP en POD verder uitgebreid en gekeken naar de onderliggende associatie. Deze studie omvatte 277 opeenvolgende patiënten die in electieve setting een vaatchirurgische ingreep hebben ondergaan. Deze analyse werd gedaan onafhankelijk van het type operatie, leeftijd of comorbiditeit. Zestien patiënten (6%) ontwikkelden een POD gedurende de ziekenhuisopname. De type operaties die werden uitgevoerd waren open aorta chirurgie (N=36, 13%), endovasculaire procedures (N=74, 26%), periphere bypasses (N=85, 31%), percutane interventies (N=43, 15%), amputaties (N=30, 11%) en overigen (N=9, 3%). De incidentie van POD was 6% in deze studie. Echter, deze bleek sterk afhankelijk van het type chirurgie dat was uitgevoerd. De hoogste incidentie (95%CI) werd gevonden na open aorta chirurgie en amputaties, 17% (4-29) en 20% (5-35), respectivelijk. De algehele conditie bij ontslag was duidelijk slechter voor patienten die een POD hadden doorgemaakt. Eenendertig procent (95%CI, 14-56%) van de patienten met POD moest naar een lang verblijf zorginstelling worden ontslagen in vergelijking met slechts 3% (95%CI, 2-6%) zonder POD (P= .0001). Na univariate analyse bleek niet alleen een verhoogd CRP (P= .001) significant gerelateerd met het optreden van POD maak ook de aanwezigheid van meerdere multiple comorbiditeiten, IC opname en open aorta en amputatie chirurgie. Multivariate logistische regressie analyse bevestigde dat een verhoogd CRP significant gecorreleerd was met het optreden van POD. De sensitiviteits analyse leverde een vergelijkbaar resultaat op. Op basis van bovengenoemde odds ratios van berekend worden dat het risico op POD met 35% stijgt indien het CRP 50 mg/L betreft en met ongeveer 90% bij een CRP concentratie van 100 mg/L (vergeleken met een CRP waarde van 5 mg/L). Deze studie toonde niet alleen aan dat het bepalen van de

CRP-waarde belangrijke informatie geeft over het risico voor het optreden van POD, maar ook dat POD is geassocieerd met een hoog risico op latere langdurige zorgbehoefte. Dit legt een verdere nadruk op de verstrekkende gevolgen van POD en de verbetering die bereikt kan worden indien adequate preventie kan worden bereikt.

Discussie

Dit proefschrift laat zien dat oudere patienten geschikt zijn om vaatchirurgie te ondergaan. Hoewel duidelijke risicofactoren zijn vastgesteld, in het bijzonder met betrekking tot het optreden van POD, lijkt het veilig deze kwetsbare groep te opereren. Echter, een belangrijke vraag blijft onbeantwoord. In dit proefschrift hebben we niet gekeken naar de kosteneffectiviteit van de behandeling van oudere patienten. In een tijd van fincanciele onzekerheid en crisis, is het niet ondenkbaar dat er beperkingen worden opgelegd, zowel in termen van ziekenhuisopname en operatie kosten.

Met de leeftijd van 80 jaar is de kans op het ondergaan van een chirurgische ingreep 35.3%. En die patiënten die een operatie ondergaan hebben een hoger gemiddeld aantal ziekenhuisopname dagen, in vergelijking met die opgenomen zonder een chirurgische ingreep, en liggen bijna twee keer zo lang op de inensive care.[17] Dit heeft een enorme impact op medische kosten en middelen. Hoewel dit tot op heden alleen nog is onderzocht voor heupchirurgie, hebben comorbiditeiten een significante invloed op de ziekenhuiskosten en de verblijfsduur.[18] Het lijkt voor de hand te liggen dat dit ook geldt voor vaatchirurgische patiënten want dit is juist een groep die bekend staat om zijn comorbidteiten Wat wel reeds bekend is is dat er hoge kosten verbonden zijn aan vaat-gerelateerde ziekenhuisopnamen met hoge tarieven voor heropname en bijkomende kosten voor patiënten met perifeer arterieel vaatlijden.[19] Ondanks dat dit proefschrift goede resultatent beschrijft na EVAR kan men vraagtekens zetten bij de kosten en de voordelen. Met het huidige klimaat van kostenbeheersing en de teruglopende vergoedingen in de gezondheidszorg, lijkt een kritische analyse van de kosten ten opzichte van de relatieve voordelen steeds belangrijker te worden. En zeker bij de behandeling van tachtigjarigen, waar de mediane overleving beperkt is door de natuurlijke levensverwachting. Uit de huidige literatuur blijkt duidelijk dat EVAR aanzienlijk duurder is in vergelijking met de open benadering. En ondanks de kortere IC- en ziekenhuisopname duur compenseert dit de hoge EVAR kosten niet.[20] Met de verdere afname van de vergoedingen kan de mogelijkheid om de kosten te dekken worden bedreigd. Omdat langdurige follow-up noodzakelijk is na EVAR, zullen de extra kosten die hiermee gepaard gaan het kostenverschil tussen EVAR en open uitschakeling verder doen oplopen.[21]

In **hoofdstuk 4** zijn de verschillen tussen CAS en CEA in tachtigjarigen reeds uitgebreid besproken. En naast de verschillen in uitkomst zijn er ook hier grote verschillen in kosten die in overweging moeten worden genomen. Kosten-effect analyses geven aanzienlijk hogere totale en directe kosten ten nadele van CAS in vergelijking met CEA. Dit verschil lijkt met name bepaald te worden door het gebruik van dure materialen.[22] Daarnaast zijn de kosten van carotis chirurgie bij ouderen al aanzienlijk hoger dan die van jongere patienten als gevolg van een groter risico op ernstige complicaties in de ouderen groep.[23] Onlangs concludeerde een grote vergelijkende effectiviteits analyse, gestratificeerd naar leeftijd, dat het wijdverbreide gebruik van CAS bij ouderen moet worden ontmoedigd door een slechtere 30-dagen uitkomst.[24] En rekening houdend met de hoge kosten, lijkt CAS geen rol te hebben in de behandeling van een carotisstenose in tachtigjarigen.

In de Verenigde Staten is de chirurgische intensiteit in het laatste levensjaar sterk gerelateerd aan het aantal ziekenhuisbedden per hoofd van de bevolking.[17] Nederland heeft 3 ziekenhuisbedden per 1000 inwoners. De verwachting is dat dit in 2015 gdaald is naar 2 per 1000 inwoners.[25] Dit zal leiden tot capaciteitsbeperkingen en waarschijnlijk tot het stellen van prioriteiten. Dit zal zeer waarschijnlijk negatieve gevolgen hebben voor de behandeling van oudere patienten, mits dezelfde trend gevolgd wordt als in de Verenigde Staten.

Maar als er keuzes worden gemaakt met betrekking tot leeftijd, is er dan ook een grens? Want geleidelijk verschijnen er steeds meer artikelen die laten zien dat negentigjarigen, onder bepaalde condities, ook prima en veilig te behandelen zijn. Maar of een levensverwachting van 1-2 jaar, met de groeiende financiele beperkingen van onze gezondheidszorg, bepalend is in de keuze van de behandeling, wordt nu meestal besloten op individuele basis. Maar met de continue verbetering van technieken en patiëntenzorg zullen steeds meer tachtig- en negentigjarigen geschikt lijken voor (grote) chirurgie. In de toekomst zullen vergelijkende effectiviteits en kosten-baten-evaluatie een steeds belangrijkere rol gaan spelen. En als de hoge kosten van EVAR niet zullen afnemen, lijkt zijn toekomst onzeker in de behandeling van oudere patiënten.

Toekomstperspectieven

Dit manuscript beschrijft de eerste stappen in de behandeling van oudere patiënten in de vaatchirurgie. Hoewel deze studie laat zien dat deze kwetsbare groep met uitstekend resultaat behandeld kan worden zijn er meer onderzoeken nodig om dit te kunnen bevestigen. In de toekomst zullen ook oudere patiënten moeten gaan deelnemen aan gerandomiseerde trials, mede omdat deze patiënten categorie in de komende tien jaar in toenemende mate deel zullen uitmaken van de algemene medische populatie. Het zijn juiste de resultaten van deze trials die van toepassing moeten zijn op de oudere patiënt om hiermee de medische besluitvorming, in deze toch moeilijke patiënten categorie, te ondersteunen.

Met de betrekking tot behandeling en preventie van POD staan we nog in de kinderschoenen. Hoewel de etiologie steeds duidelijker is geworden lijkt de echte winst te liggen in de preventie. De GFI kan een belangrijke rol gaan spelen in de nabije toekomst maar moet verder worden ontwikkeld voor vaatchirurgische patiënten. Met een aangepaste score en een passend pre-/postoperatief interventie plan lijkt er veel te winnen. Daarnaast lijkt CRP eveneens een belangrijke rol te spelen en onderzoek naar de etiologie van die relatie kan verder inzicht verschaffen in het optreden en daarmee ook voorkomen van POD. Deze kwesties zullen onze aandacht hebben in de toekomst en hopelijk bijdragen tot een veiligere en efficiëntere behandeling van oudere patiënten.

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CHAPER 10

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Prof Dr. C.J.A.M. Zeebregts: Beste Clark, vanaf de eerste dag dat ik bij je aan het bureau stond is de promotie trein gaan rijden en niet meer tot stilstand gekomen. Zonder jouw hulp, inzet en tomeloos vertrouwen zou dit proefschrift in dit tempo er niet geweest zijn. Van de 2 A4-tjes met een eerste opzet en indeling is uiteindelijk alleen het eerste hoofdstuk voortgekomen. De rest lijkt eigenlijk uit de vrije hand ontstaan waarbij er aan ideeën nooit gebrek bleek. Dit proces was geweldig om mee te maken en hierin ben je altijd de motor geweest. Ik heb je snelle correcties en vlijmscherpe opmerkingen vervloekt en ervan gehouden maar altijd hield je de vaart er in. Ik heb ongelofelijk veel van je geleerd en wil je heel hartelijk bedanken voor je inzet en het getoonde vertrouwen en ik reken op een nog heel vruchtbare samenwerking in de toekomst!

Dr. B.L. van Leeuwen: Beste Barbara, jouw inbreng heeft misschien nog wel de meeste kleur gegeven aan dit proefschrift. Dat ik onderzoek naar delier zou doen en er zelfs uiteindelijk op zou promoveren kon ik mij enkele jaren geleden niet voorstellen. Je enthousiasme, nuchtere en soms relativerende kijk heeft niet alleen geleid tot prachtige resultaten maar ook tot een boekje waar ik enorm trots op ben. Je hebt mij aangestoken met het 'Ageing' virus en mijn ogen geopend voor een sterk onderbelicht maar belangrijk onderwerp. Daarvoor wil ik je hartelijk bedanken. Fijn dat je bij de openbare verdediging als copromotor aanwezig bent.

Dr. M.M.P.H. Reijnen: Beste Michel, terwijl ik mijn handen al vol had aan Clark werd er in Arnhem een 2e diesel motor opgestart. Hoewel hierdoor mijn mailbox soms overstroomde van actieve dialogen en ideeën, kwam de sneltrein hiermee echt op gang. Je hebt op meerdere vlakken de totstandkoming van dit proefschrift niet alleen een impuls maar ook richting gegeven. Ik wil je bedanken voor de geweldige samenwerking en begeleiding en voor het feit dat je mijn copromotor wilt zijn. We hebben nog een project lopen en ik betwijfel of het daarbij zal blijven.

Beste co-auteurs: Bedankt voor jullie inzet, samenwerking en vertrouwen. Zonder jullie hulp was dit proefschrift er niet geweest. Ik kon altijd rekenen op scherpe commentaren die uiteindelijk hebben geleid tot een aantal prachtige artikelen.

Dr G.J. Izaks: Beste Gerbrand, als internist ouderengeneeskunde (geriater) ben je betrokken geweest bij een aantal projecten. Daarmee was je een goede tegenhanger voor al het chirurgisch geweld en enthousiasme rond het tot stand komen van dit boekje. Je wist soms terecht op de rem te trappen om het daarna weer snel de juiste richting te geven. Je heldere kijk, bereidwilligheid, didactiek en geduld heb ik erg gewaardeerd en ik hoop dat we in de toekomst nog vaak zullen samenwerken.

Dr. J.J.A.M. van den Dungen: Beste Jan, met een nuchtere kijk en een gezonde scepsis zijn een aantal manuscripten voor dit proefschrift je bureau gepasseerd. En steeds werd dit weer voorzien van de vraagtekens over de klinische toepasbaarheid. Maar ik geloof dat ik je inmiddels wel heb overtuigd omdat ouderen, delier en delier preventie steeds vaker onderwerp van gesprek waren tijdens grote visites en vaatbesprekingen. Ik wil je bedanken voor je medewerking en je vertrouwen in mij als CHIVO.

Drs. C. Krikke: Beste Christina, nu word je eindelijk een keer bedankt in een proefschrift. Als hoofd van de afdeling transplantatie chirurgie heb je mij als fellow niet alleen een geweldige baan maar ook kans gegeven. Je hebt mij hiermee de ruimte gegeven om dit proefschrift te voltooien maar ook de mogelijkheid geboden om te doen wat ik graag wil doen. Ik ben er trots op dat je mijn vervolgopleider bent!

Leden van de beoordelingscommissie: Hartelijk dank voor het beoordelen van dit proefschrift en deelname aan de oppositie.

Beste Dick: Al bijna 34 jaar mag ik je mijn vriend noemen. Dat je nu actief betrokken bent geweest bij de lay-out en ontwerp van dit boekje vind ik heel bijzonder. Je hebt van droge tekst en tabellen een prachtig boekje weten te maken wat ik een uitzonderlijke prestatie vind. Dank je wel voor je hulp en trouwe vriendschap.

Collega arts-assistenten: Dit proefschrift had niet tot stand kunnen komen zonder mijn ongeremd ventileren in de assistentenkamer. En dan nog maar te zwijgen over mijn gezeur over statistische toetsen, p-waarden, mislukte analyses en SPSS-problemen die toch wekelijks de revue passeerden. Daarnaast heb ik jullie, op een al dampende vaat afdeling, ook nog extra administratie gegeven door het laten invullen van data formulieren e.d. Hiervoor mijn dank en een mooi feestje!

Beste paranimfen Dr. R.J.H. Custers en M. Blankestijn:
Roel, ik kan mij na ons afstuderen nog goed herinneren wat ik dacht toen jij als arts-onderzoeker bij de orthopedie ging werken. Drie jaar achter een bureau in plaats van de kliniek in? Ik wist wel beter. Maar nu ik het schrijven van mijn thesis en de opleiding heb proberen te combineren ben ik jouw volgorde steeds meer gaan benijden. Maar ook mijn boekje is af en ik zou met niemand anders de laatste stappen willen zetten.
Michael, ik ben al vergeten hoe lang wij elkaar nu kennen. Maar inmiddels beiden trotse vaders en aan een nieuwe fase in ons leven begonnen. Bijna alle hoogte- en dieptepunten uit mijn leven hebben we samen doorgemaakt en deze promotie mag daaraan niet ontbreken. Ik ben ongelofelijk trots dat je naast mij staat.

Maaike: Mijn lief, mijn alles. Wat ben ik ongelooflijk blij met jou aan mijn zijde. Dit proefschrift behoort ook aan jou want je hebt het lief en leed met mij mogen delen. Hoe weinig je er ook over sprak, ik weet hoe blij je bent met de voltooiing van dit boekje.
"Sometimes your nearness takes my breath away; and all things I want to say can find no voice. Then in silence, I can only hope my eyes will speak my heart." (Robert Sexton)

Olivier en Annebel: Wat ben ik blij dat jullie er zijn! Zonder het te beseffen weten jullie alles te relativeren. Ik kijk uit naar alle mooie momenten die we samen nog gaan hebben. Papa houdt van jullie.

CHAPER 11

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CHAPER 12

CURRICULUM VITAE

Robert Pol was born on March 28th 1978 in Apeldoorn, The Netherlands. Robert attended high school at de Heemgaard from which he graduated in 1996. Then he began to study biomedical chemistry for one year at the Rijkshogeschool IJsselland. After completing the propaedeutic phase he decided to switch studies and started his medical study at the Utrecht University. In 2004 he graduated from medical school and started as a surgical and intensive care resident in the Isala Clinics in Zwolle, The Netherlands. After 2 years he was accepted for his surgical residency where he spent the first 4 years at the Deventer hospital (Dr. M. Eeftinck Schattenkerk). During this period he published several papers dealing with several different topics. In 2010 he continued his surgical training at the University Medical Centre in Groningen (Prof Dr H.J. ten Duis). The same year he started his research on vascular surgery in elderly patients, under supervision of Prof Dr C.J.A.M. Zeebregts, which resulted in this thesis.

Currently Robert is working at the University Medical Centre in Groningen as a fellow in transplantation surgery (Drs C. Krikke) and as CHIVO (surgeon in follow-up training) (Dr. J.J.A.M. van den Dungen) in vascular surgery.

Robert is married with Maaike and they have 2 children (Olivier and Annebel).

APPENDIX

LETTERS TO THE EDITOR

In this section are two published "letters to the editors" on two different papers. In the first letter we respond to the report by Raval et al. in Surgery. 2012;151:245-260. We responded to this paper because we felt that the article fell short on two important points. Although they described one of the largest series of octogenarians with AAA, they do not answer the question whether their conclusions also apply to octogenarians experiencing acute AAA? Also they do not describe nor discuss where the border for treatment is with regard to age? We feel that these are important questions when dealing with octogenarians.

In the second letter we respond to the report by Biancari et al. in the World J Surg. 2011;35:1662-1670. They report on the outcome after open repair of ruptured abdominal aortic aneurysm (RAAA) in patients > 80 years old. We felt the article is inadequate in answering important questions. For instants, they do not mention the positive outcome after endovascular repair (EVAR) in this vulnerable group. Current data, including our own results in **Chapter 2**, show that the surgical mortality after RAAA repair is justified in octogenarians. Secondly, there is a significant difference in hospital length of stay, ICU length of stay, in-hospital and overall mortality in favour of EVAR compared to open repair. So given the good long-term prognosis of octogenarians after successful repair, even attempts of open repair seems justified.

LETTER I

RE: "OUTCOMES OF ELECTIVE ABDOMINAL AORTIC ANEURYSM REPAIR AMONG THE ELDERLY: ENDOVASCULAR VERSUS OPEN REPAIR"

Robert A. Pol
Michel M.P.J. Reijnen
Clark J. Zeebregts

Surgery. 2011;149:855-856

Dear Sir,

We have read with great interest the report by Raval and Eskandari describing the national outcome data after open (OSR) and endovascular repair (EVAR) of elective abdominal aortic aneurysms (AAA) in octogenarians.[1] They describe one of the largest series of octogenarians with AAA and report a significant better overall morbidity and mortality in patients < 80 years. Furthermore, octogenarians were more likely to be treated by EVAR which resulted in a significantly better morbidity and mortality compared to OSR. In our centres, we also treat octo- and nonagenarians with AAA, both in the elective and acute setting.[2,3] On most parts we agree with the authors; however, two important questions remain unanswered: (1) Do their conclusions also apply to octogenarians experiencing acute AAA? and (2). Where is the limit for treatment with regard to age?

In a recent study focussing on octogenarians with acute AAA, we found a median survival of more than 2.8 years for octogenarians, although intensive care (ICU) and hospital durations of stay were not prolonged compared with younger patients. (mean ICU stay 6.9 ± 11.5 days for patients < 80 years and 5.7 ± 7.8 days for octogenarians (P=.33); mean hospital stay, 16.9 ± 20.4 days for patients < 80 years and 13.7 ± 16.7 days for octogenarians (P= .11).[3] We observed no differences in procedure- and disease-related complications between the two groups. Consistent with the results by Raval and Eskandari we found a significant difference in hospital and ICU duration of stay, and in-hospital and overall mortality in favour of EVAR compared with OSR. Unfortunately, Raval and Eskandari do not report on the outcome of acute AAAs. Especially in acute cases, advanced age may be considered a contraindication to further treatment, especially when EVAR is not feasible, leaving OSR the only treatment option.

Despite the reported good results, we feel that there are limits to the usefulness of treatment in the elderly. Although age alone is not a reason to refrain from treatment, current evidence merely confirms that octogenarians may be safely treated by EVAR. But where are the limits and what happens if we include nonagenarians? Two recent publications dealing with this issue concluded that, despite advanced age, these patients do benefit from intervention at very acceptable morbidity and mortality rates.[2,4] However, all patients who presented with an acute AAA died after treatment. It, therefore, seems that age per se is far less important than, for example, the biological condition of the patients, which is drawn from the severity and quantity of both the disease and comorbidities.

One must conclude that there are certainly upper limits to the treatable age and they are mainly determined by urgency and treatment options, in this case, suitability for EVAR. Although for octo- and nonagenarians, in an elective setting, an acceptable survival may be achieved after OSR, this does not apply to emergent cases and should therefore be discouraged in these situations.

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LETTER II

OUTCOME AFTER OPEN REPAIR OF RUPTURED ABDOMINAL AORTIC ANEURYSM IN PATIENTS >80 YEARS OLD: A SYSTEMATIC REVIEW AND META-ANALYSIS

Robert A. Pol
Michel M.P.J. Reijnen
Clark J. Zeebregts

World J Surg. 2011;35:2575-2576

Dear Sir,

We have read with great interest the report by Biancari et al.[1] on the outcome after open repair of ruptured abdominal aortic aneurysm (RAAA) in patients older than 80 years old. We agree with their conclusions on the acceptable survival rates for open repair of RAAA in octogenarians. We also have extensive experience treating both octo- and nonagenarians with (R)AAA at comparable survival rates as reported by Biancari et al.[2,3] We therefore encourage proper research within this patient group to gain more insight into possibilities and limitations that may be encountered. Although we understand that a certain time limit was set for the inclusion and drafting of their manuscript, we feel our own published papers could have added relevant information to the discussion and should have been added to the meta-analysis. Second, we feel that the article falls short in answering important questions regarding some specific features. Although they clearly show that octogenarians with a RAAA can be treated conventionally, they do not mention the positive outcome after endovascular repair (EVAR) in this vulnerable group. Both our study, as well as a recent publication on one of the largest series of octogenarians with AAA, found a significant difference in hospital length of stay, ICU length of stay and in-hospital and overall mortality in favour of EVAR compared with open repair.[3,4] In another report, designed to define cost-effectiveness of a preferential endovascular strategy in patients with RAAA, we found that in-hospital mortality dropped from 31% (historical open repair control group) to 18% (for endovascular repair of selected patients). Even reports on nonagenarians concluded that despite advanced age, these patients may benefit from an intervention at acceptable morbidity and mortality rates after EVAR.[2,5] For reasons of a potential selection bias, EVAR patients were excluded from the current analysis. Especially for the elderly, a short hospitalization period and quick return to the former level of functioning is of vital importance. These are all benefits of endovascular repair. We therefore believe that this should be the first treatment option. Various studies made clear that octogenarians were often labelled unfit for open repair due to significant comorbidities and consequently were offered EVAR. These important criteria applicable in elective setting may be even more important with a devastating event, such as RAAA. Whereas frequent and accurate monitoring for endoleak development or stent graft migration is essential after EVAR in a younger population, these are of much less importance in the elderly with a natural limited life expectancy. In conclusion, octogenarians affected by RAAA can be safely treated by open or endovascular repair. However, the preferred treatment of choice should be EVAR, because octogenarians benefit most from its minimal invasive character and short-term hospitalization. In case of hemodynamic instability or unsuitable anatomy for EVAR, patients with a good baseline functional status can be offered open repair with a median survival of 2.8 years.[3]

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